Effekt av tiltak for å avslutte legemiddelavhengighet

Notat
Litteratursøk med sortering
Oktober 2009

kunnskapssenteret

Bakgrunn: Nasjonalt kunnskapssenter for helsetjenesten har på oppdrag fra Helsedirektoratet gjort et litteratursøk med sortering for problemstillingen "Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?". **Resultat:** Vi identifiserte totalt 63 mulig relevante oversiktsartikler. Vi har presentert dem i henhold til type avhengighet. Artiklene er ikke innhentet i fulltekst eller vurdert for kvalitet i form av risiko for systematiske skjevheter/metodiske svakheter.

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Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Senteret er formelt et forvaltningsorgan under Helsedirektoratet, uten myndighetsfunksjoner. Kunnskapssenteret kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten
Oslo, oktober 2009

1-side oppsummering

Det er kjent at pasienter har utviklet legemiddelavhengighet etter lovlig bruk av vanedannende legemidler (anxiolytika, analgetika, og hypnotika). Dette kalles av noen for ”lavdose-avhengighet”. Begrepet er ikke entydig definert, og er gjenstand for uenighet i fagmiljøene.

Med bakgrunn i Legemiddelmeldingen skal Helsedirektoratet kvantifisere problemområdet, bidra til økt oppmerksomhet rundt feilaktig – men også riktig bruk av denne type legemidler og sikre et felles begrepsapparat/definisjoner på legemiddelavhengighet.

Helsedirektoratet ønsker derfor en oversikt over litteratur som kan være til hjelp i arbeidet. I samarbeid med Kunnskapssenteret ble det laget to problemstillinger som lot seg løse ved hjelp av vår metodologi.

1) Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?

2) Effekt av tiltak for å hindre at pasienter blir legemiddelavhengige (for eksempel effekt av ulike forskrivningsmønster).

Denne rapporten er et søk med etterfølgende sortering av identifisert litteratur for problemstilling nummer 1.

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Publikasjoner som omhandlet benzodiazepinavhengige 15
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Publikasjoner fra håndsøk 63

Forord

Nasjonalt kunnskapssenter for helsetjenesten fikk januar 2009 i oppdrag fra Helsedirektoratet å identifisere litteratur om emnet: Legemiddelavhengig men ikke rusmisbruker. Problemstillingen ble omformulert til "Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?"

Nasjonalt kunnskapssenter for helsetjenesten har svart på denne oppgaven ved å gjøre et systematisk litteratursøk etterfulgt av sortering av relevante publikasjoner i forhold til spørsmålet. Arbeidet med denne rapporten er utført av en intern arbeidsgruppe ved Nasjonalt kunnskapssenter for helsetjenesten:

- Prosjektleder: Forsker Tove Ringerike
- Prosjektmedarbeider: Hege Kornør
- Prosjektmedarbeider: Forskningsbibliotekar Ingrid Harboe
- Prosjektansvarlig: Forskningsleder Marianne Klemp

Gro Jamtvedt	Marianne Klemp	Tove Ringerike
Avdelingsdirektør	*Forskningsleder*	*Forsker, prosjektleder*

Problemstilling

- Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?

Innledning

Det er kjent at pasienter har utviklet legemiddelavhengighet etter bruk av vanedannende legemidler (anxiolytika, analgetika og hypnotika) forskrevet på lovlig vis. Dette kalles av noen for "lavdose-avhengighet". Begrepet er ikke entydig definert, og er gjenstand for uenighet i fagmiljøene.

Med bakgrunn i Legemiddelmeldingen skal Helsedirektoratet kvantifisere problemområdet, bidra til økt oppmerksomhet rundt feilaktig – men også riktig bruk av denne type legemidler og sikre et felles begrepsapparat/definisjoner på legemiddelavhengighet.

Helsedirektoratet ønsker derfor en oversikt over litteratur som kan være til hjelp i arbeidet. I samarbeid med Kunnskapssenteret ble det laget to problemstillinger som lot seg løse ved hjelp av vår metodologi.

1) Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?

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Denne rapporten er et søk med etterfølgende sortering av identifisert litteratur for problemstilling nummer 1.

Metode

Problemstillingen i denne rapporten er løst som et litteratursøk med påfølgende sortering av relevant litteratur. Med bakgrunn i problemstillingen har vi valgt å begrense søket til oversiktsartikler.

LITTERATURSØK

Vi la bestillingen til grunn ved utarbeiding av litteratursøket og søkte etter oversikter som oppfylte våre inklusjonskriterier for populasjon og intervensjon.

Vi søkte systematisk etter litteratur i følgende databaser 23. juli 2009:

- EMBASE 1980 to 2009 week 29
- MEDLINE (In-process & Other Non-Indexed Citations and Ovid medline 1950 to present)
- Centre for Reviews and Dissemination
- The Cochrane Library

Det ble brukt filter for systematiske oversikter. I de tilfeller det var mulig valgte vi det filteret med høyest spesifisitet. Emneord og tekstord i litteratursøket ble satt sammen av en bibliotekar etter diskusjon med oppdragsgiver og prosjektgruppen.

Vi utførte også håndsøk etter relevant litteratur hos andre organisasjoner som lager oversikter og medisinske metodevurderinger. Rapporter fra slike organisasjoner blir ikke alltid indeksert i Medline. Håndsøk ble gjort i National Institute for Health and Clinical Excellence (NICE), Danish Centre for Evaluation and Health Technology Assessment (DACEHTA), Finnish Office for Health Technology Assessment (Finohta) og Statens beredning för medicinsk utvärdering (SBU).

INKLUSJONSKRITERIER

Populasjon:	Legemiddelavhengige
Intervensjoner:	Benzodiazepiner, anxiolytika, analgetika, hypnotika og opioider
Utfall:	Effekt av tiltak for å avslutte avhengighet

Studiedesign: Oversiktsartikler
Språk: Ingen begrensninger

UTVELGELSE OG SORTERING

To forskere gikk gjennom alle titler og sammendrag for å vurdere relevans i henhold til inklusjonskriteriene. Vurderingene ble gjort uavhengig av hverandre og sammenlignet i etterkant. Der det var uenighet om vurderingene, ble inklusjon eller eksklusjon avgjort ved konsensus.

Utvelgelse av litteratur ble kun gjort basert på tittel og sammendrag. Vi bestilte ikke fulltekst av artiklene.

Resultat

RESULTAT FRA SØKET

Søk etter litteratur ble utført 23. juli 2009 av forskningsbibliotekar Ingrid Harboe. Søkestrategiene finnes i vedlegg 1.

Søket identifiserte 715 unike referanser (1072 før dublettkontroll). Vi vurderte 60 publikasjoner som relevante. De ble sortert i tre kategorier basert på type avhengighet: benzodiazepinavhengige (5 publikasjoner), andre legemidler og kombinasjoner av legemidler (11 publikasjoner) og opioidavhengige (44 publikasjoner). I vedlegg 2 presenterer vi referansene alfabetisk etter førsteforfatter. Vi oppgir forfattere, tittel på publikasjonen, publikasjonssted og abstrakt av artikkelen slik de fremkom i de elektroniske databasene.

De vanligste eksklusjonsgrunnene var at studiene ikke undersøkte ulike måter å seponere pågående behandling / avhengighet eller at de så på risiko for avhengighet.

Ved håndsøk hos utvalgte andre organisasjoner som lager oversikter og medisinske metodevurderinger identifiserte vi ytterligere tre mulig relevante publikasjoner. De presenteres også i vedlegg 2 i et eget avsnitt med tittel, omtale og tilhørende lenke til publikasjonen.

Diskusjon

Problemstillingen vi har søkt etter litteratur for å besvare er:

- Hvilke tiltak er mest effektive i behandling av legemiddelavhengige pasienter med den hensikt å få dem til å avslutte avhengigheten?

Vi har utført et systematisk litteratursøk og sortert identifisert litteratur i forhold til våre inklusjonskriterier. Vi gjør spesielt oppmerksom på at det medførte eksklusjon av publikasjoner som omhandlet behandling av abstinens/withdrawal symptomer, substitusjonsbehandling for eksempel fra et opioid til et annet, tilbakefallsforebygging etter avsluttet legemiddelseponering og vurdering av risikofaktorer for utvikling av avhengighet. I resultatene har vi presentert studiene etter type avhengighet (benzodiazepinavhengige, andre legemidler og kombinasjoner av legemidler og opioidavhengige,). Sorteringen er kun basert på tittel og sammendrag. Vi har ikke lest eller bestilt artiklene i fulltekst.

Fremgangsmåten som benyttes i prosjekter av typen litteratursøk med sortering har utfordringer knyttet til seg. Manglende innhenting av artikler i fulltekst gjør at vi kan ha inkludert titler som vil vise seg ikke å være relevante ved gjennomlesning av fulltekst. På den annen side kan vi ha utelatt studier som bestiller muligens ville betraktet som relevante fordi kriteriene vi har sortert etter ikke fremgår av tittel eller sammendrag. Manglede innhenting av relevante artikler i fulltekst umuliggjør også en vurdering av studienes kvalitet i form av risiko for systematiske skjevheter/metodiske svakheter og dermed en fremstilling av hvorvidt det er aspekter ved studiene som stiller spørsmålstegn ved troverdigheten til resultatene.

Bestiller får i tillegg til vår rapport overlevert RefMan databasen med søket før sortering slik at de om ønsket kan gå mer detaljert inn i dette.

Vedlegg 1 – Søkestrategier

SØKESTATEGI I EMBASE

EMBASE 1980 to 2009 Week 29

#	Searches	Results
1	Morphine addiction/ or Opiate addiction/	6261
2	exp Benzodiazepine Derivative/	99356
3	exp Anxiolytic Agent/	98347
4	exp Opiate Agonist/	181832
5	exp Hypnotic Sedative Agent/	171948
6	(benzodiazepin$ or anxiolyt$ or anti-anxiet$ or antianxiet$ or anti anxiet$ or opiate$ or opioid$ or hypnotic$ or sedative$ or hypnosedative$ or morphin$ or hydromorphon$ or oxycodon$ or codein$ or ketobemidon$ or pethidin$ or fentanyl$ or dextropropoxyphen$ or buprenorphin$ or methadon$ or tramadol$ or diazepam$ or oxazepam$ or alpra-zolam$ or nitrazepam$ or flunitrazepam$ or midazolam$ or zopiclon$ or zolpidem$ or clozapin$ or carisoprodol$).tw.	149360
7	or/2-6	395490
8	Addiction/	5288
9	Withdrawal Syndrome/	11541
10	(addict$ or depend$ or misus$ or abus$).tw.	1087284
11	withdraw$.tw.	64448
12	Drug dependence/	25005
13	((drug or substance) adj2 (addict$ or depend$ or misus$ or abus$ or withdraw$)).tw.	37552
14	or/8-13	1147960
15	7 and 14	74153
16	1 or 15	75338
17	limit 16 to "reviews (2 or more terms high specificity)"	270

SØKESTRATEGI I COCHRANE LIBRARY

Cochrane Reviews [67] | Other Reviews [42] | Clinical Trials [2613] | Methods Studies [8] | Technology Assessments [13] | Economic Evaluations [56] | Cochrane Groups [0]
Dato: 23.07.2009

ID	Search	Hits
#1	MeSH descriptor Opioid-Related Disorders explode all trees	897
#2	MeSH descriptor Benzodiazepines explode all trees	6851
#3	MeSH descriptor Anti-Anxiety Agents explode all trees	7598
#4	MeSH descriptor Receptors, Opioid explode all trees	274
#5	MeSH descriptor Hypnotics and Sedatives explode all trees	9437
#6	(benzodiazepin* or anxiolyt* or anti-anxiet* or antianxiet* or anti anxiet* or opiate* or opioid* or hypnotic* or sedative* or hypnosedative* or morphin* or hydromorphon* or oxycodon* or codein* or ketobemidon* or pethidin* or fentanyl* or dextropropoxyphen* or buprenorphin* or methadon* or tramadol* or diazepam* or oxazepam* or alprazolam* or nitrazepam* or flunitrazepam* or midazolam* or zopiclon* or zolpidem* or clozapin* or carisoprodol*):ti,ab,kw	30506
#7	(#2 OR #3 OR #4 OR #5 OR #6)	34744
#8	MeSH descriptor Substance-Related Disorders, this term only	1831
#9	MeSH descriptor Substance Withdrawal Syndrome, this term only	1418
#10	(addict* or depend* or misus* or abus*):ti,ab kw	91
#11	withdraw*:ti,ab,kw	10126
#12	((drug or substance) near/2 (addict* or depend* or misus* or abus* or withdraw*)):ti,ab,kw	5361
#13	(#8 OR #9 OR #10 OR #11 OR #12)	14020
#14	(#7 AND #13)	2449
#15	(#1 OR #14)	2799

SØKESTRATEGI I CRD

All results (423), DARE (265), NHS EED (131), HTA (27)
Dato: 23.07.2009

# 1	MeSH Opioid-Related Disorders EXPLODE 1 2	80
# 2	MeSH Benzodiazepines EXPLODE 1	222
# 3	MeSH Anti-Anxiety Agents EXPLODE 1 2 3	48
# 4	MeSH Receptors, Opioid EXPLODE 1 2 3	8

#	5	MeSH Hypnotics and Sedatives EXPLODE 1 2 3 4	101
#	6	benzodiazepin* OR anxiolyt* OR anti-anxiet* OR antianxiet* OR anti AND anxiet* OR opiate* OR opioid* OR hypnotic* OR sedative* OR hypnosedative* OR morphin* OR hydromorphon* OR oxycodon* OR codein* OR ketobemidon* OR pethidin* OR fentanyl* OR dextropropoxyphen* OR buprenorphin* OR methadon* OR tramadol* OR diazepam* OR oxazepam* OR alprazolam* OR nitrazepam* OR flunitrazepam* OR midazolam* OR zopiclon* OR zolpidem* OR clozapin* OR carisoprodol*	1064
#	7	#2 OR #3 OR #4 OR #5 OR #6	1238
#	8	MeSH Substance-Related Disorders	294
#	9	MeSH Substance Withdrawal Syndrome	37
#	10	addict* OR depend* OR misus* OR abus*	3538
#	11	withdraw*	1833
#	12	#8 OR #9 OR #10 OR #11	5186
#	13	#7 and #12	408
#	14	#1 or #13	423

SØKESTRATEGI I MEDLINE

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present
Dato: 23.07.2009

#	Searches	Results
1	Morphine Dependence/ or Opioid-Related Disorders/	8667
2	exp Benzodiazepines/	52249
3	exp Anti-Anxiety Agents/	51539
4	exp Receptors, Opioid/	19443
5	exp "Hypnotics and Sedatives"/	92583
6	(benzodiazepin$ or anxiolyt$ or anti-anxiet$ or antianxiet$ or anti anxiet$ or opiate$ or opioid$ or hypnotic$ or sedative$ or hypnosedative$ or morphin$ or hydromorphon$ or oxycodon$ or codein$ or ketobemidon$ or pethidin$ or fentanyl$ or dextropropoxyphen$ or buprenorphin$ or methadon$ or tramadol$ or diazepam$ or oxazepam$ or alprazolam$ or nitrazepam$ or flunitrazepam$ or midazolam$ or zopiclon$ or zolpidem$ or clozapin$ or carisoprodol$).tw.	159900
7	or/2-6	243968

8	Substance-Related Disorders/	64410
9	Substance Withdrawal Syndrome/	16522
10	(addict$ or depend$ or misus$ or abus$).tw.	1313014
11	withdraw$.tw.	73264
12	[Drug dependence/ => Substance-Related Disorders]	0
13	((drug or substance) adj2 (addict$ or depend$ or misus$ or abus$ or withdraw$)).tw.	43905
14	or/8-13	1401560
15	7 and 14	50732
16	1 or 15	53719
17	limit 16 to "reviews (specificity)"	428

Vedlegg 2 – Sortering av relevante publikasjoner

PUBLIKASJONER SOM OMHANDLET BENZODIAZEPINAVHENGIGE

1. Busto UE, Pain T, Lanctot KL, Einarson TR, Naranjo CA. Assessment of the risk of therapeutic dose benzodiazepine withdrawal reactions with meta-analysis. Canadian Journal of Clinical Pharmacology 1998;5(3):161-8.
   Ref ID: 242
   Abstract: OBJECTIVE: To quantify and clarify the risk of experiencing withdrawal symptoms upon discontinuation of long term therapeutic dose use of selected benzodiazepines compared with that of discontinuation of placebo. METHODS: A meta-analysis of all trials published on withdrawal syndrome upon discontinuation of diazepam, alprazolam and triazolam was conducted. Data were collected on the proportion of patients reporting withdrawal symptoms after abrupt and gradual discontinuation of these medications. Variables used for the meta-analysis were rate of occurrence of anxiety, insomnia and memory lapse when discontinuing diazepam; panic attacks, anxiety and phobia when discontinuing alprazolam; and sleep latency, total sleep time, wake time after sleep onset and number of awakenings after sleep onset when discontinuing triazolam. Random effects models for meta-analysis were used to synthesize the data. Each article was also rated for quality (1 = poor, 5 = excellent). RESULTS: The pooled mean of the risk ratio of withdrawal syndrome upon abrupt discontinuation of long term therapeutic dose diazepam (95% CI) for studies with a high quality score (4 or greater) was 3.12 (range 2.83 to 3.44). Risk ratios for individual symptoms ranged from 1.1 (nausea) to 4.71 (anxiety). When the meta-analysis included all studies the risk ratio was 8.0 (range 5.94 to 17.55). Gradual discontinuation of diazepam lowered the risk ratio of withdrawal syndrome to 1.26 (range 1.15 to 1.40). Data could not be extracted from alprazolam discontinuation studies. The risk differences of sleep disturbances after discontinuation of therapeutic doses of triazolam for studies with a high quality score varied widely depending on the symptom, from 19.85 (range 15.48 to 24.23) for rebound insomnia to -3.11 (range -5.46 to 0.76) for sleep latency. As with diazepam, risk differences of sleep disturbances increased when lower quality studies were included in the analysis. CONCLUSIONS: When diazepam and triazolam are administered at therapeutic doses for periods of days to a few weeks, the risk of experiencing withdrawal symptoms is modest. Thus, withdrawal reactions upon discontinuation of benzodiazepines should not limit their use for

appropriate indications because in most cases the risk of dependence is low and therapeutic benefit may outweigh the risk of dependence

2. Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database of Systematic Reviews 2006;(3):CD005194.
   Ref ID: 785
   Abstract: BACKGROUND: The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Although benzodiazepines are highly effective for some disorders, they are potentially addictive drugs and they can provide reinforcement in some individuals. OBJECTIVES: To evaluate the effectiveness of pharmacological interventions for benzodiazepine mono-dependence. SEARCH STRATEGY: We searched the Cochrane Drugs and Alcohol Group' Register of Trials (October 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (January 1966 to October 2004), EMBASE (January 1988 to October 2004), PsycInfo (1985 to October 2004), CINAHL (1982 to October 2004), Pascal, Toxibase, reference lists of articles. SELECTION CRITERIA: Randomized trials of benzodiazepines dependence management regardless of type, dose (daily and total) and duration of f therapy and type of therapy. DATA COLLECTION AND ANALYSIS: Reviewers independently assessed trials for inclusion, rated their methodological quality and extracted data. MAIN RESULTS: 753 references were selected and 35 were eligible. Eight met the inclusion criteria for a total of 458 participants. The studies included could not be analysed cumulatively because of heterogeneity of interventions and participants' characteristics. Results support the policy of gradual rather than abrupt withdrawal of benzodiazepine. Progressive withdrawal (over 10 weeks) appeared preferable if compared to abrupt since the number of drop-outs was lower and the procedure judged more favourable by the participants. Short half-life benzodiazepine, associated with higher drop-out rates, did not have higher withdrawal symptoms scores. Switching from short half-life benzodiazepine to long half-life benzodiazepine before gradual taper withdrawal did not receive much support from this review. No benefits of Propanolol, Dothiepin, Buspirone, Progesterone or Hydroxyzine were found for managing benzodiazepine withdrawal or improving benzodiazepine abstinence. Carbamazepine might have promise as an adjunctive medication for benzodiazepine withdrawal, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or more of diazepam (or equivalents). AUTHORS' CONCLUSIONS: All included studies showed that gradual taper was preferable to abrupt discontinuation. The results of this systematic review point to the potential value of carbamazepine as an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated. Other treatment approaches to benzodiazepine discontinuation management should be explored (antidepressants, benzodiazepine receptors modulator). PHARMACOLOGICAL INTERVENTIONS FOR BENZODIAZEPINE MONO-DEPENDENCE MANAGEMENT IN OUTPATIENT SETTINGS: The improved safety profile of benzodiazepines compared to bar-

biturates has contributed to a high rate of prescription since the seventies. Prevalence of benzodiazepines use remains important worldwide. Although benzodiazepines are highly effective as short-term treatments for some disorders, they also are potentially addictive drugs. This review has shown that a gradual taper is preferable to abrupt discontinuation of benzodiazepines, and that carbamazepine may be an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated

3. Fatseas M, Lavie E, Denis C, Franques-Reneric P, Tignol J, Auriacombe M. [Benzodiazepine withdrawal in subjects on opiate substitution treatment]. Presse Med 2006;35(4 Pt 1):599-606.
   Ref ID: 414
   Abstract: INTRODUCTION: Benzodiazepines are the most widely used psychotropic agents in the world. Abuse and dependence are reported in the general population and among drug misusers, including those dependent on heroine. Benzodiazepine use by heroine users increases their risk of overdose, not only from heroin but also substitution drugs such as methadone and more recently buprenorphine. Hence, detoxification from benzodiazepines is desirable. OBJECTIVE: The objective of this paper was to review the literature and determine the best benzodiazepine detoxification procedure for opiate-dependent individuals receiving substitution treatment. METHODS: Relevant studies were sought through systematic searches of Medline and Toxibase (a database focusing on substance abuse). RESULTS: There were fewer controlled studies than expected about benzodiazepine detoxification, and all of them excluded subjects who misused opiates or were in opiate substitution treatment. The best evidence supports a procedure where the patient is switched to a long-lasting benzodiazepine and the dose then tapered by 25% of the initial dose each week. Diazepam is the drug most often used in the framework. In opiate users, diazepam may raise special problems of misuse, as suggested by clinical and epidemiologic studies. Nonetheless, diazepam is the only benzodiazepine found to be effective for this withdrawal in controlled studies and some studies indicate that unprescribed diazepam use in heroin users is sometimes motivated by the desire to alleviate withdrawal symptoms and discomfort. CONCLUSION: Although diazepam appears to have potential for abuse, the available data does not rule out its therapeutic interest for benzodiazepine withdrawal in patients on opiate substitution treatment in an adequate treatment setting. Specific studies of this population are needed. [References: 44]

4. Parr JM, Kavanagh DJ, Cahill L, Mitchell G, McD Young R. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. Addiction 2009;104(1):13-24.
   Ref ID: 301
   Abstract: AIMS: To assess the effectiveness of current treatment approaches to assist benzodiazepine discontinuation. METHODS: A systematic review of approaches to benzodiazepine discontinuation in general practice and out-patient settings was undertaken. Routine care was compared with three treatment approaches: brief interventions, grad-

ual dose reduction (GDR) and psychological interventions. GDR was compared with GDR plus psychological interventions or substitutive pharmacotherapies. RESULTS: Inclusion criteria were met by 24 studies, and a further eight were identified by future search. GDR [odds ratio (OR) = 5.96, confidence interval (CI) = 2.08-17.11] and brief interventions (OR = 4.37, CI = 2.28-8.40) provided superior cessation rates at post-treatment to routine care. Psychological treatment plus GDR were superior to both routine care (OR = 3.38, CI = 1.86-6.12) and GDR alone (OR = 1.82, CI = 1.25-2.67). However, substitutive pharmacotherapies did not add to the impact of GDR (OR = 1.30, CI = 0.97-1.73), and abrupt substitution of benzodiazepines by other pharmacotherapy was less effective than GDR alone (OR = 0.30, CI = 0.14-0.64). Few studies on any technique had significantly greater benzodiazepine discontinuation than controls at follow-up. CONCLUSIONS: Providing an intervention is more effective than routine care. Psychological interventions may improve discontinuation above GDR alone. While some substitutive pharmacotherapies may have promise, current evidence is insufficient to support their use. [References: 61]

5. Voshaar RCO, Couvee JE, van Balkom AJLM, Mulder PGH, Zitman FG. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. Br J Psychiatry 2006;189:213-20.
   Ref ID: 397
   Abstract: BACKGROUND: The prevalence of benzodiazepine consumption in European countries remains at 2-3% of the general population despite the well-documented disadvantages of long-term use. AIMS: To review systematically the success rates of different benzodiazepine discontinuation strategies. METHOD: Meta-analysis of comparable intervention studies. RESULTS: Twenty-nine articles met inclusion criteria. Two groups of interventions were identified; minimal intervention (e.g. giving simple advice in the form of a letter or meeting to a large group of people; n=3), and systematic discontinuation (defined as treatment programmes led by a physician or psychologist; n=26). Both were found to be significantly more effective than treatment as usual: minimal interventions (pooled OR=2.8, 95% CI 1.6-5.1); systematic discontinuation alone (one study, OR=6.1, 95% CI 2.0-18.6). Augmentation of systematic discontinuation with imipramine (two studies, OR=3.1, 95% CI 1.1-9.4) or group cognitive-behavioural therapy for patients with insomnia (two studies, OR=5.5, 95% CI 2.3-14.2) was superior to systematic discontinuation alone. CONCLUSIONS: Evidence was found for the efficacy of stepped care (minimal intervention followed by systematic discontinuation alone) in discontinuing long-term benzodiazepine use. [References: 47]

PUBLIKASJONER SOM OMHANDLET ANNEN AVHENGIGHET ENN BENZODIAZEPINER OG OPIOIDER ELLER OMHANDLET BLANDINGSMISBRUK

1. Alexander CN, Robinson P, Rainforth M. Treating and preventing alcohol, nicotine, and drug abuse through transcendental meditation: A review and statistical meta-analysis.

Alcoholism Treatment Quarterly 1994;11(1-2):13-87.
Ref ID: 258

2. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry 2008;165(2):179-87.
Ref ID: 339
Abstract: OBJECTIVE: Despite significant advances in psychosocial treatments for substance use disorders, the relative success of these approaches has not been well documented. In this meta-analysis, the authors provide effect sizes for various types of psychosocial treatments, as well as abstinence and treatment-retention rates for cannabis, cocaine, opiate, and polysubstance abuse and dependence treatment trials. METHOD: With a comprehensive series of literature searches, the authors identified a total of 34 well-controlled treatment conditions-five for cannabis, nine for cocaine, seven for opiate, and 13 for polysubstance users-representing the treatment of 2,340 patients. Psychosocial treatments evaluated included contingency management, relapse prevention, general cognitive behavior therapy, and treatments combining cognitive behavior therapy and contingency management. RESULTS: Overall, controlled trial data suggest that psychosocial treatments provide benefits reflecting a moderate effect size according to Cohen's standards. These interventions were most efficacious for cannabis use and least efficacious for polysubstance use. The strongest effect was found for contingency management interventions. Approximately one-third of participants across all psychosocial treatments dropped out before treatment completion compared to 44.6% for the control conditions. CONCLUSIONS: Effect sizes for psychosocial treatments for illicit drugs ranged from the low-moderate to high-moderate range, depending on the substance disorder and treatment under study. Given the long-term social, emotional, and cognitive impairments associated with substance use disorders, these effect sizes are noteworthy and comparable to those for other efficacious treatments in psychiatry

3. Hesse M, Vanderplasschen W, Rapp R, Broekaert E, Fridell M. Case management for persons with substance use disorders. Cochrane Database of Systematic Reviews 2007;(4):CD006265.
Ref ID: 754
Abstract: BACKGROUND: Patients with alcohol and other drug use disorders (AOD) frequently have multiple social, physical, and mental health treatment needs, yet have difficulty accessing community services, including drug abuse treatment. One strategy for linking patients with AOD with relevant services is case management, where a single case manager is responsible for linking patients with multiple relevant services. OBJECTIVES: To conduct a systematic review of all RCTs on the use of case management for helping drug abusers in or out of treatment. Outcome criteria included successful linkage with other services, illicit drug use outcomes, and a range of related outcomes. SEARCH STRATEGY: We searched the Cochrane Controlled Trials Register (Cochrane Library, issue 4, 2006), MEDLINE (1966 - 2006), EMBASE (1980 - 2006), LILACS (1982 - 2006), PsycINFO (1973 - 2006), Biological Abstracts (1982 t- 2000). Reference searching; personal communication; conference abstracts; book chapters on case management. SE-

LECTION CRITERIA: Randomized controlled studies that compared a specific model of case management with either treatment as usual or another treatment model, included only patients with at least one alcohol or drug related problem. DATA COLLECTION AND ANALYSIS: Two groups of reviewers extracted the data independently . Standardized mean difference was estimated. MAIN RESULTS: In total, we could extract results from 15 studies. Outcome on illicit drug use was reported from 7 studies with 2391 patients. The effect size for illicit drug use was not significant, and small (standardized mean difference (SMD)=0.12, confidence interval=-0.09,0.29, p=0.20). Substantial heterogeneity was found (I2=69.9%). Linkage to other treatment services was reported in 10 studies with 3132 patients. The effect size for linkage was moderate (SMD=0.42, 95% confidence interval=0.21 to 0.62, p<0.001), but substantial heterogeneity was found (I2=85.2%). Moderator analyses suggested that a part of the heterogeneity found in linkage studies could be explained by the presence or absence of a treatment manual for case management. A single, large trial of case management with two arms, showed that case management was superior to psycho education and drug counselling in reducing drug use. AUTHORS' CONCLUSIONS: There is current evidence supporting that case management can enhance linkage with other services. However, evidence that case management reduces drug use or produce other beneficial outcome is not conclusive. ILLICIT USE OF DRUGS SUCH AS OPIOIDS, COCAINE, AMPHETAMINES, CANNABIS AND ALCOHOL DEPENDENCE HAVE HEALTH, SOCIAL AND ECONOMIC COMPLICATIONS. USERS OFTEN HAVE LONG-TERM PROBLEMS IN ADDITION TO SUBSTANCE ABUSE. CASE: management is a client-centred strategy involving assessment, planning, linking to relevant services and community resources and advocacy. Its intent is to improve the co-ordination and continuity of delivery of services. Brokerage case management sets out to help clients identify their needs and broker services in one or two contacts; intensive case management involves a closer interaction between case manager and client; assertive community treatment (provides assertive outreach and direct counselling services; strengths-based case management focuses on self-direction and the use of informal networks rather than agency resources by applying active outreach. From this review, case management effectively linked people with substance abuse to community and treatment services as compared to treatment as usual or other viable treatment options, such as psycho-education or brief interventions. This conclusion is based on 10 randomised controlled trials involving 3132 participants that compared case management to usual treatment. Two studies compared case management with other specific treatments. Additional analysis of the studies suggested that the use of a manual to guide the delivery of case management could increase linkage. A total of 15 controlled studies that randomised a total of 6694 participants were included in the review. One study was conducted in Europe; all other studies were from North America. Seven studies with 2391 participants did not find a clear reduction in illicit drug use with case management compared with usual treatment; similarly with alcohol use (two studies). A single, large trial showed that case management for heroin users was superior to psycho-education and drug counselling in reducing drug use. The extent of linkage varied significantly between studies, which is likely to be influenced by the availabil-

ity of services in the community, the model of case management, how effectively it is applied and its integration in the local network of services

4. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging 2008;25(12):1021-31.
   Ref ID: 309
   Abstract: The objective of this review was to assess the benefits and risks of medication withdrawal in older people as documented in published trials of medication withdrawal. This was done by systematic review of the evidence from clinical trials of withdrawal of specific classes of medications in patient populations with a mean age of >or=65 years. We identified all relevant articles published between 1966 and 2007 initially through electronic searches on PubMed and manual searches of review articles. Numerous search terms related to the withdrawal of medication in older people were utilized. Clinical trials identified were reviewed according to predetermined inclusion/exclusion criteria. Only trials that focused on the withdrawal of specific classes of medication were included. Thirty-one published studies (n = 8972 subjects) met the inclusion criteria, including four randomized and placebo-controlled studies (n = 448 subjects) of diuretic withdrawal, nine open-label and prospective observational studies (n = 7188 subjects) of withdrawal of antihypertensives (including diuretics), 16 studies (n = 1184 patients) of withdrawal of sedative, antidepressant, cholinesterase inhibitor and antipsychotic medications, and 1 study each of withdrawal of nitrates and digoxin. These studies were of heterogeneous study design, patient selection criteria and follow-up. Withdrawal of diuretics was maintained in 51-100% of subjects and was unsuccessful primarily when heart failure was present. Adverse effects from medication withdrawal were infrequently encountered. After withdrawal of antihypertensive therapy, many subjects (20-85%) remained normotensive or did not require reinstatement of therapy for between 6 months and 5 years, and there was no increase in mortality. Withdrawal of psychotropic medications was associated with a reduction in falls and improved cognition. In conclusion, there is some clinical trial evidence for the short-term effectiveness and/or lack of significant harm when medication withdrawal is undertaken for antihypertensive, benzodiazepine and psychotropic agents in older people. [References: 73]

5. McCarthy G, Myers B, Siegfried N. Treatment for Methaqualone dependence in adults. Cochrane Database of Systematic Reviews 2005;(2):CD004146.
   Ref ID: 807
   Abstract: BACKGROUND: Methaqualone is a potent quinazoline, a class of sedative-hypnotics, that has a high potential for abuse. While the oral use of methaqualone (Quaalude, Mandrax) has waned in western countries since the mid-late 1980's, the practice of smoking methaqualone is a serious public health problem in South Africa, other parts of Africa and India. In the context of diminishing resources devoted to substance abuse treatment in regions affected by methaqualone abuse, it would be desirable to base treatment on the best evidence available. This review aimed to provide health care workers, policy-makers and consumers with the necessary information to make decisions regarding effective treatment of this highly dependence-producing drug.

OBJECTIVES: To compare the effectiveness of any type of pharmacological or behavioural treatment administered in either an in-patient or out-patient setting compared with either a placebo or no treatment or a waiting list, or with another form of treatment administered in either an in- or out-patient setting. SEARCH STRATEGY: The authors searched the following databases: Cochrane Drugs and Alcohol Group'Register of Trials (February 2004); Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, Issue 2, 2004); MEDLINE (OVID - January 1966 to February 2004), PsycInfo (OVID - January 1967 to February 2004). Relevant conference proceedings and reference lists of relevant articles were hand-searched. Broad Internet searches were conducted and contact made with experts in the field. SELECTION CRITERIA: All randomised controlled trials and quasi-randomised trials of the effectiveness of treatment programmes (in- or out-patient) for methaqualone dependence and abuse were considered for inclusion in this review. DATA COLLECTION AND ANALYSIS: The authors independently assessed study eligibility and quality. MAIN RESULTS: No studies were found that met the inclusion criteria. AUTHORS' CONCLUSIONS: To date, no randomized controlled trials appear to have been conducted. Consequently, the effectiveness of inpatient versus outpatient treatment, psychosocial treatment versus no treatment, and pharmacological treatments versus placebo for methaqualone abuse or dependence has yet to be established. THERE IS CURRENTLY NO EVIDENCE TO DETERMINE THE BEST WAY TO TREAT MANDRAX DEPENDENCE IN ADULTS.: Dependence and abuse of methaqualone, a type of sedative-hypnotic, is a major public health problem in parts of Africa and India. Treatment is highly variable and takes place in both in-patient and out-patient settings. Despite an extensive search of electronic databases, the internet, relevant conferences and contact with experts in the field, this review identified no randomised controlled trials of the effectiveness of treatment for Mandrax dependence and/or abuse. Currently no evidence exists for using one type of treatment over another

6. Prendergast ML, Podus D, Chang E. Program factors and treatment outcomes in drug dependence treatment: an examination using meta-analysis. Subst Use Misuse 2000;35(12-14):1931-65.
   Ref ID: 613
   Abstract: In comparison with studies of client characteristics and treatment processes, limited research has been conducted on how program features of drug dependence treatment programs may affect client outcomes. Of particular interest are those characteristics of programs that may have a clinically significant impact on outcomes and that are amenable to change within programs. This study examines the impact of various program factors on client outcomes using data from a meta-analysis of drug dependence effectiveness studies (n = 143). Because of heterogeneity among studies, the data are analyzed in terms of type of outcome variable (drug use and crime), type of design (single-group and treatment-comparison group), and type of treatment (methadone maintenance, therapeutic communities, outpatient drug free, and detoxification). For the more valid treatment-comparison group studies, the weighted mean effect size was 0.29 for drug use outcomes and 0.17 for crime outcomes. Program factors found to be significantly correlated with effect size in one or more modalities were decade of treatment, re-

searcher involvement in treatment delivery, maturity of the program, counselor/client ratio, treatment implementation, treatment exposure, and methadone dosage

7. Prendergast ML, Podus D, Chang E, Urada D. The effectiveness of drug abuse treatment: A meta-analysis of comparison group studies. Drug Alcohol Depend 2002;67(1):53-72.
   Ref ID: 214
   Abstract: A meta-analysis was conducted on 78 studies of drug treatment conducted between 1965 and 1996. Each study compared outcomes among clients who received drug treatment with outcomes among clients who received either minimal treatment or no treatment. Five methodological variables were significant predictors of effect size. Larger effect sizes were associated with studies with the following characteristics: smaller numbers of dependent variables, significant differences between groups at admission, low levels of attrition in the treatment group, a passive comparison group (no treatment, minimal treatment) as opposed to an active comparison group (standard treatment), and drug use determined by a drug test. Controlling for these methodological variables, further analyses indicated that drug abuse treatment has both a statistically significant and a clinically meaningful effect in reducing drug use and crime, and that these effects are unlikely to be due to publication bias. For substance abuse outcomes, larger effect sizes tended to be found in studies in which treatment implementation was rated high, the degree of theoretical development of the treatment was rated low, or researcher allegiance to the treatment was rated as favorable. For crime outcomes, only the average age of study participants was a significant predictor of effect size, with treatment reducing crime to a greater degree among studies with samples consisting of younger adults as opposed to older adults. Treatment modality and other variables were not related to effect sizes for either drug use or crime outcomes copyright 2002 Elsevier Science Ireland Ltd. All rights reserved

8. Tang YL, Hao W. Improving drug addiction treatment in China. Addiction 2007;102(7):1057-63.
   Ref ID: 363
   Abstract: AIMS: To illustrate the current situation and problems of drug addiction in treatment China and propose suggestions. METHODS: A descriptive study based on literature searched from Medline and the China National Knowledge Infrastructure database (1996-2007) and hand-picked references. RESULTS: Since the re-emergence of drug addiction in China in the early 1990s, there has been tremendous progress in drug addiction treatments in China, especially treatments for opiate addiction. However, many problems and challenges remain for improvement, including widespread negative attitudes towards drug abuse and drug-dependent individuals, the lack of evidence-based data on the efficacy of Chinese traditional medicine and the lack of a comprehensive and integrated system to organize all treatment resources and monitor treatment progress. The authors discuss the challenges that impede effective treatments of drug addiction and some suggestions are proposed. Implementing these suggestions can improve the outcome of treatment of drug-dependent individuals and benefit the whole society. CONCLUSION: China faces substantial drug addiction problems that appear to be worsening

with time. Although much progress in drug addiction treatment has been made, improvement in many aspects is needed urgently. [References: 61]

9. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 2000;28(6):2122-32.
   Ref ID: 624
   Abstract: OBJECTIVE: To describe the consequences of the prolonged administration of sedative and analgesic agents to the pediatric intensive care unit (PICU) patient. The problems to be investigated include tolerance, physical dependency, and withdrawal. DATA SOURCES: A MEDLINE search was performed of literature published in the English language. Cross-reference searches were performed using the following terms: sedation, analgesia with PICU, children, physical dependency, withdrawal; tolerance with sedative, analgesics, benzodiazepines, opioids, inhalational anesthetic agents, nitrous oxide, ketamine, barbiturates, propofol, pentobarbital, phenobarbital. STUDY SELECTION: Studies dealing with the problems of tolerance, physical dependency, and withdrawal in children in the PICU population were selected. DATA EXTRACTION: All of the above-mentioned studies were reviewed in the current manuscript. DATA SYNTHESIS: A case by case review is presented, outlining the reported problems of tolerance, physical dependency, and withdrawal after the use of sedative/analgesic agents in the PICU population. This is followed up by a review of the literature discussing current treatment options for these problems. CONCLUSIONS: Tolerance, physical dependency, and withdrawal can occur after the prolonged administration of any agent used for sedation and analgesia in the PICU population. Important components in the care of such patients include careful observation to identify the occurrence of withdrawal signs and symptoms. Treatment options after prolonged administration of sedative/analgesic agents include slowly tapering the intravenous administration of these agents or, depending on the drug, switching to subcutaneous or oral administration. [References: 76]

10. Von Sydow K, Beher S, Retzlaff R, Schweitzer-Rothers J. Systemic therapy for adult index patients. Psychotherapeut 2007;52(3):187-211.
    Ref ID: 86
    Abstract: Background. Systemic therapy is a scientifically acknowledged form of psychotherapy in the US and many European countries, but not yet in Germany. Method. All randomized (or parallelized) controlled trials (RCT) evaluating systemic couples/family/individual therapy with adult index patients published in English, German or Spanish up to the end of 2004 were identified via data base searches and cross-references in other meta-analyses and reviews. A meta-analysis of the identified RCT was performed. Results. 28 RCT (43 publications) evaluating systemic therapy with adult index patients suffering from clinical disorders (ICD-10) were identified. Systemic therapy is efficacious with regard to substance disorders, mental/social factors interacting with somatic disorders, schizophrenia, depression and eating disorders. The results are stable across follow-up periods of up to 5 years. Conclusion. According to the criteria of the German Scientific Advisory Board Psychotherapy (Wissenschaftlicher Beirat Psycho-

therapie) there seems to be good evidence for the efficacy of systemic therapy in at least four fields of application of adult psychotherapy. copyright 2005 Springer Medizin Verlag

11. Wobrock T, Soyka M. Pharmacotherapy of schizophrenia with comorbid substance use disorder--reviewing the evidence and clinical recommendations. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(6):1375-85.
    Ref ID: 318
    Abstract: Substance use disorder is the most common psychiatric comorbidity in schizophrenic patients, with prevalence rates of up to 65%. Recommendations for antipsychotic pharmacotherapy in schizophrenia are based on studies that excluded patients with this dual diagnosis. In the present comprehensive systematic review, the pharmacological studies performed in this subgroup of patients are summarised and discussed from the standpoint of evidence-based medicine. Unfortunately, randomized controlled studies, providing a high evidence level, in patients with this dual diagnosis are rare. Data, mainly based on open studies or case series, suggest superior efficacy for second generation antipsychotic agents (SGAs) (aripiprazole, clozapine, olanzapine, quetiapine, risperidone) with regard to improvement of distinct psychopathological symptoms, reduced craving and greater reduction of substance use compared with orally administered conventional antipsychotics (FGAs). Tricyclic antidepressants given adjunctive to antipsychotic maintenance therapy showed efficacy in reducing substance use and craving. The administration of anti-craving agents (naltrexone) led to a decrease of drug intake. Unfortunately, there is no clinical experience with acamprosate in schizophrenic patients with comorbid alcoholism. In conclusion, there are more theoretically based arguments for the preferential use of SGAs in schizophrenic patients with comorbid substance use disorder while the empirical evidence is weak. The early initiation of treatment with antidepressants, depending on the patient's psychopathology, as well as add-on medication with anti-craving agents should be considered. [References: 99]

PUBLIKASJONER SOM OMHANDLET OPIOIDAVHENGIGE

1. Effective medical treatment of opiate addiction. JAMA 1998;280(22):1936-43.
    Ref ID: 650
    Abstract: OBJECTIVE: To provide clinicians, patients, and the general public with a responsible assessment of the effective approaches to treat opiate dependence. PARTICIPANTS: A nonfederal, nonadvocate, 12-member panel representing the fields of psychology, psychiatry, behavioral medicine, family medicine, drug abuse, epidemiology, and the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 600. Presentations and discussions were divided into 3 phases over 2 1/2 days: (1) presentations by investigators working in the areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of a third day. The conference was organized and supported by

the Office of Medical Applications of Research, National Institutes of Health. EVIDENCE: The literature was searched through MEDLINE and other National Library of Medicine and online databases from January 1994 through September 1997 and an extensive bibliography of 941 references was provided to the panel and the conference audience. Experts prepared abstracts for their presentations as speakers at the conference with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience. CONSENSUS PROCESS: The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions. CONCLUSIONS: Opiate dependence is a brain-related medical disorder that can be effectively treated with significant benefits for the patient and society, and society must make a commitment to offer effective treatment for opiate dependence to all who need it. All persons dependent on opiates should have access to methadone hydrochloride maintenance therapy under legal supervision, and the US Office of National Drug Control Policy and the US Department of Justice should take the necessary steps to implement this recommendation. There is a need for improved training for physicians and other health care professionals. Training to determine diagnosis and treatment of opiate dependence should also be improved in medical schools. The unnecessary regulations of methadone maintenance therapy and other long-acting opiate agonist treatment programs should be reduced, and coverage for these programs should be a required benefit in public and private insurance programs. [References: 63]

2. Amato L, Davoli M, Ferri M, Gowing L, Perucci CA. Effectiveness of interventions on opiate withdrawal treatment: an overview of systematic reviews. Drug Alcohol Depend 2004;73(3):219-26.
   Ref ID: 514
   Abstract: AIM: To provide an overview of 5 Cochrane reviews of different approaches for treating opioid withdrawal. DESIGN: Narrative and quantitative summary of review findings. PARTICIPANTS: There were 46 studies included in the original reviews with a total of 3350 participants (range 18-300). INTERVENTION: The 5 reviews considered 46 studies covering seven different comparisons, the major ones being methadone compared with alpha2-adrenergic agonists and other opioid agonists, different alpha2-adrenergic agonists compared with each other and to antagonist-induced withdrawal and buprenorphine. MEASUREMENTS: The outcomes considered were signs and symptoms of withdrawal, retention in treatment, completion rate, relapse rate and side effects. FINDINGS: Methadone detoxification results in higher retention in treatment, lower relapse rate and fewer side effects when compared with adrenergic agonists. No difference was observed when comparing different adrenergic agonists; buprenorphine appears to have an advantage over adrenergic agonists on withdrawal symptoms and side

effects. CONCLUSIONS: Despite the considerable number of trials that have been carried out on this topic, they are very heterogeneous as far as the comparisons and outcomes considered. This prevented many of them from being incorporated into a quantitative meta-analysis. Consensus in measurements and results should be reached among researchers involved in the evaluation of the effectiveness of treatments for opiate addiction in order to produce consistent outcomes in the measuring and reporting of results from clinical trials

3. Amato L, Davoli M, Minozzi S, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2005;(3):CD003409.
   Ref ID: 770
   Abstract: BACKGROUND: Despite widespread use in many countries the evidence of tapered methadone's efficacy in managing opioid withdrawal has not been systematically evaluated. OBJECTIVES: To evaluate the effectiveness of tapered methadone compared with other detoxification treatments and placebo in managing opioid withdrawal on completion of detoxification and relapse rate. SEARCH STRATEGY: We searched: Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2008), PubMed (January 1966 to December 2007), EMBASE (January 1988 to December 2007), CINAHL (2003- December 2007), PsycINFO (January 1985 to December 2004), reference lists of articles. SELECTION CRITERIA: All randomised controlled trials which focus on the use of tapered methadone versus all other pharmacological detoxification treatments or placebo for the treatment of opiate withdrawal. DATA COLLECTION AND ANALYSIS: Two reviewers assessed the included studies. Any doubt about how to rate the studies were resolved by discussion with a third reviewer. Study quality was assessed according to the criteria indicated in Cochrane Reviews Handbook 4.2. MAIN RESULTS: Twenty trials involving 1907 people were included. Comparing methadone versus any other pharmacological treatment we observed no clinical difference between the two treatments in terms of completion of treatment, relative risk (RR) 1.08 (95% CI 0.95 to 1.24) and results at follow-up RR 1.17 (95% CI 0.72 to 1.92). It was impossible to pool data for the other outcomes but the results of the studies did not show significant differences between the considered treatments. These results were confirmed also when we considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (five studies), anxiolytic (two studies). Comparing methadone with placebo (two studies) more severe withdrawal and more drop outs were found in the placebo group. The results indicate that the medications used in the included studies are similar in terms of overall effectiveness, although symptoms experienced by participants differed according to the medication used and the program adopted. AUTHORS' CONCLUSIONS: Data from literature are hardly comparable; programs vary widely with regard to the assessment of outcome measures, impairing the application of meta-analysis. The studies included in this review confirm that slow tapering with temporary substitution of long acting opioids, can reduce withdrawal severity. Nevertheless the majority of patients relapsed to heroin use. METHADONE AT TAPERED DOSES FOR THE MANAGEMENT OF OPIOID WITHDRAWAL: Abuse of opioid drugs and dependence on

them causes major health and social issues that include transmission of HIV and hepatitis C, increased crime and costs for health care and law enforcement, family disruption and lost productivity. Addicts, particularly those aged 15 to 34 years, are also at higher risk of death. Managed withdrawal (or detoxification) is used as the first step in treatment. Withdrawal symptoms include anxiety, chills, muscle pain (myalgia) and weakness, lethargy and drowsiness and various pharmacological agents can be used to reduce them. Persisting sleep disturbances and drug craving can continue for weeks and months after detoxification and often lead to relapse to opioid use. The number of addicts who complete detoxification tends to be low, and rates of relapse to opioid use following detoxification are high. For a tapered dose treatment, illicit opioids are substituted with methadone or another agent under medical supervision in decreasing doses. The review authors searched the medical literature and identified 16 controlled trials involving 1187 adult opioid users in various countries. Trial participants were randomised to receive methadone or another pharmacological treatment over 3 to 30 days. The other treatments were adrenergic agonists including clonidine (11 studies), opioid agonists such as buprenorphine and LAAM (four studies) and chlordiazepoxide (one study). In the one study that compared methadone with placebo, withdrawal symptoms were more severe and more drop outs were found in the placebo group. The methadone starting dose ranged from 20 to 58 mg/day (mean 29 mg/day). Withdrawal symptoms were reduced with methadone but the majority of people relapsed to heroin use. There was no clear difference in completion of treatment or abstinence at follow up with the different agents. The results indicate that the medications used in the included studies are similar in terms of overall effectiveness although symptoms experienced by participants differed according to the medication used and the program adopted. Treatment with adrenergic agonists was associated with lower mean blood pressure (postural hypotension) than with methadone, from five trials

4. Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database of Systematic Reviews 2008;(4):CD005031.
   Ref ID: 788
   Abstract: BACKGROUND: Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless a majority of patients relapse to heroin use, and relapses are a substantial problem in the rehabilitation of heroin users. Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological rather than physiological symptoms associated with the withdrawal syndrome. OBJECTIVES: To evaluate the effectiveness of any psychosocial plus any pharmacological interventions versus any pharmacological alone for opioid detoxification, in helping patients to complete the treatment, reduce the use of substances and improve health and social status. SEARCH STRATEGY: We searched the Cochrane Drugs and Alcohol Group trials register (27 February 2008). Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2008), PUBMED (1996 to February 2008); EMBASE (January 1980 to February 2008); CINAHL (January 2003-February 2008); PsycINFO (1985 to April 2003) and reference list of articles. SE-

LECTION CRITERIA: Randomised controlled trials which focus on any psychosocial associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded. DATA COLLECTION AND ANALYSIS: Three reviewers independently assessed trials quality and extracted data. MAIN RESULTS: Nine studies involving people were included. These studies considered five different psychosocial interventions and two substitution detoxification treatments: Methadone and Buprenorphine. The results show promising benefit from adding any psychosocial treatment to any substitution detoxification treatment in terms of completion of treatment relative risk (RR) 1.68 (95% confidence interval (CI) 1.11 to 2.55), use of opiate RR 0.82 (95% CI 0.71 to 0.93), results at follow-up RR 2.43 (95% CI 1.61 to 3.66), and compliance RR 0.48 (95% CI 0.38 to 0.59). AUTHORS' CONCLUSIONS: Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, results at follow-up and compliance. Although a treatment, like detoxification, that exclusively attenuates the severity of opiate withdrawal symptoms can be at best partially effective for a chronic relapsing disorder like opiate dependence, this type of treatment is an essential step prior to longer-term drug-free treatment and it is desirable to develop adjunct psychosocial approaches that might make detoxification more effective. Limitations to this review are imposed by the heterogeneity of the assessment of outcomes. Because of lack of detailed information no meta analysis could be performed to analyse the results related to several outcomes. PSYCHOSOCIAL AND PHARMACOLOGICAL TREATMENTS VERSUS PHARMACOLOGICAL TREATMENTS FOR OPIOID DETOXIFICATION: People who abuse opioid drugs and become dependent on them experience social issues and health risks. Medications such as methadone and buprenorphine are substituted to help dependent drug users detoxify and return to living drug free, by reducing physiological withdrawal symptoms (pharmacological detoxification). Yet psychological symptoms can occur during detoxification and may be distressing. It is often a personal crisis that led to a drug user deciding to detoxify. Furthermore the psychological reasons why a person became addicted are important. They may not be able to cope with stress and have come to expect that using mood modifying illicit substances helps. Even after successful return to a drug-free state, many people return to heroin use and re-addiction is a substantial problem in rehabilitation. The physiological, behavioural and social conditions in an individual's life that made them an opiate addict may still be present when physical dependence on the drug has been eliminated, which makes psychosocial therapy important. Psychosocial treatments include behavioural treatments, counselling and family therapy. The review authors searched the medical literature and found evidence that providing a psychosocial treatment in addition to pharmacological detoxification treatment to adults who are dependent on heroin use is effective in facilitating opioid detoxification. This conclusion is based on nine controlled studies involving 634 adults, 32% men, with an average age of 34 years (28 to 41 years). The studies lasted 16 days to 26 weeks. The addition of a psychosocial treatment to substitution detoxification treatment improved the number of people who completed treatment (relative risk (RR) 1.68), use of opiate (RR 0.82), abstinence from drugs at follow up (RR 2.4), and halved the number of failures to attend clinic absences (RR 0.48). The findings of an im-

proved rate of clinical attendance may help in suppressing illicit drug use and provides clinical staff with more opportunities to counsel patients in psychiatric, employment and other drug and non-drug related areas. Variations in the populations who are substance users and use of a wide range of different psychosocial interventions means that it is difficult to single out particular therapeutic interventions

5. Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database of Systematic Reviews 2008;(4):CD004147.
   Ref ID: 789
   Abstract: BACKGROUND: Maintenance treatments are effective in retaining patients in treatment and suppressing heroin use. Questions remain regarding the efficacy of additional psychosocial services offered by most maintenance programs. OBJECTIVES: To evaluate the effectiveness of any psychosocial plus any agonist maintenance treatment versus standard agonist treatment for opiate dependence in respect of retention in treatment, use of substances, health and social status. SEARCH STRATEGY: We searched: Cochrane Drugs and Alcohol Group's Register of Trials (February 2008), Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library issue 1, 2008), MEDLINE (January 1966 to February 2008), EMBASE (January 1980 to February 2008), CINAHL (January 2003-February 2008), PsycINFO (January 1985 to April 2003), reference lists of articles. SELECTION CRITERIA: Randomised studies comparing any psychosocial plus any agonist with any agonist alone intervention for opiate dependence. DATA COLLECTION AND ANALYSIS: Three reviewers independently assessed trial quality and extracted data. MAIN RESULTS: Twenty eight trials, 2945 participants, were included. These studies considered twelve different psychosocial interventions and three pharmacological maintenance treatments. Comparing any psychosocial plus any maintenance pharmacological treatment to standard maintenance treatment, results do not show benefit for retention in treatment, 23 studies, 2193 participants, Relative Risk (RR) 1.02 (95% CI 0.97 to 1.07), use of opiate during the treatment, eight studies, 681 participants, RR 0.86 (95% CI 0.65 to 1.13), compliance, three studies, MD 0.43 (95% CI -0.05 to 0.92), psychiatric symptoms, four studies, MD 0.02 (-0.19 to 0.23), depression, four studies, MD -1.30 (95% CI -3.31 to 0.72) and results at follow up as number of participants still in treatment at the end of the follow-up , 289 participants, RR 0.91 (95% CI 0.77 to 1.06). In spite of results at follow up as number of participants abstinent at the end of the follow-up, five studies, 232 participants, show a benefit in favour of the associated treatment RR1.15 (95% CI 1.01 to 1.32). The remaining outcomes were analysed only in single studies considering a limited number of participants.Comparing the different psychosocial approaches, results are never statistically significant for all the comparisons and outcomes. AUTHORS' CONCLUSIONS: Results suggest that adding any psychosocial support to maintenance treatments improve the number of participants abstinent at follow up; no differences for the other outcome measures. Data do not show differences between different psychosocial interventions also for contingency approaches, contrary to all expectations. Duration of the studies

was too short to analyse relevant outcomes such as mortality. COMBINED PSYCHO-SOCIAL AND AGONIST MAINTENANCE INTERVENTIONS FOR TREATMENT OF OPIOID DEPENDENCE: The abuse of opioid drugs and drug dependency are major health and social issues. Maintenance treatments with pharmacological agents can help to reduce the risks associated with the use of street drugs for drug addicts who are unable to abstain from drug use. Methadone is effective in retaining patients in treatment and reducing heroin use but re-addiction remains as a substantial challenge. Opiate addicts often have psychiatric problems such as anxiety and depression and may not be able to cope with stress. Psychosocial interventions including psychiatric care, psychotherapy, counselling, and social work services are commonly offered as part of the maintenance programs. Psychological support varies from structured psychotherapies such as cognitive behavioural therapy and supportive-expressive therapy to behavioural interventions and contingency management. This review addressed whether a specific psychosocial intervention provides any additional benefit to pharmacological maintenance treatment. The control intervention was a maintenance program, which routinely offers counselling sessions in addition to pharmacological treatment. Present evidence suggests that adding psychosocial support does not change the effectiveness of retention in treatment. Nor does it result in a clear reduction in opiate use during treatment. Findings on retention in treatment were for 12 different psychosocial interventions including contingency management over 6 to 48 weeks. These conclusions are based on 28 randomised trials involving 2945 opiate addicts, some 66% of whom were male. The average age was 37 years (range 27 to 45). All but two studies were conducted in the USA. The number of participants abstinent at the end of follow up (five trials) and continuous weeks of abstinence (two trials) showed a benefit in favour of the associated treatment. The previous version of this review showed a reduction in opiate use during treatment that was no longer the case with the addition of new studies. The psychosocial interventions are likely to require rigorous assessment of any changes in emotional, interpersonal, vocational and physical health areas of life functioning that may indirectly reduce drug use over longer periods of time

6. Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. Addiction 2001;96(5):683-90.
   Ref ID: 601
   Abstract: BACKGROUND: The unique pharmacological properties of buprenorphine may make it a useful maintenance therapy for opiate addiction. This meta-analysis considers the effectiveness of buprenorphine relative to methadone. METHODS: A systematic literature search identified five randomized clinical trials comparing buprenorphine to methadone. Data from these trials were obtained. Retention in treatment was analyzed with a Cox proportional hazards regression. Urinalyses for opiates were studied with analysis of variance and a common method of handling missing values. A meta-analysis was used to combine these results. RESULTS: Subjects who received 8-12 mg/day buprenorphine had 1.26 times the relative risk of discontinuing treatment (95% confidence interval 1.01-1.57) and 8.3% more positive urinalyses (95% confidence interval 2.7-14%) than subjects receiving 50-80 mg/day methadone. Buprenophrine was more effective

than 20-35 mg/day methadone. There was substantial variation in outcomes in the different trials. CONCLUSIONS: The variation between trials may be due to differences in dose levels, patient exclusion criteria and provision of psychosocial treatment. The difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the differences are small compared to the wide variance in outcomes achieved in different methadone treatment programs. Further research is needed to determine if buprenorphine treatment is more effective than methadone in particular settings or in particular subgroups of patients

7. Berglund M. A better widget? Three lessons for improving addiction treatment from a meta-analytical study. Addiction 2005;100(6):742-50.
   Ref ID: 455
   Abstract: OBJECTIVE: To discuss how to develop more effective treatment programmes than those currently available for addictive disorders. DATA SOURCES: The Swedish SBU report, published in English in 2003, was used as a database. It includes 641 randomized controlled trials and seven longitudinal prospective studies. METHODS: Meta-analytical calculations were performed in several areas using standardized mean differences (d) effect-size estimate and homogeneity testing. Three critical issues have been the focus of the present analysis: the early intervention phase, treatment procedures and their additive properties and the transitional period between early and late effects of treatment. RESULTS: The main findings while integrating the results in a new way were that intervention studies with one single session showed a small but robust homogeneous effect size, whereas studies of interventions with several sessions were heterogeneous with large and small effect sizes among the included studies. Similar effect sizes were found in alcohol, opioid and cocaine treatment studies. Agonist treatment yielded the highest effect sizes. Some evidence was found for a possible additive effect for cognitive behaviour therapy and naltrexone as well as for aversive treatment (disulfiram) and psychosocial treatment in alcohol dependence. So far studies on the transition period between short- and long-term outcome are few and inconclusive. CONCLUSIONS: There is a prospect of improving addiction treatment, and the following areas are suggested by meta-analysis for future research: (a) to examine in more detail the process between the first and second session of intervention; (b) to randomize simultaneously for independent categories of psychosocial and psychopharmacological treatment; and (c) to intensify studies on the transitional period between short- and long-term outcome

8. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 2007;11(9):1-171.
   Ref ID: 372
   Abstract: OBJECTIVES: To assess the clinical effectiveness and cost-effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) for the management of opioid-dependent individuals. DATA SOURCES: Major electronic databases were searched from inception to August 2005. Industry submissions to the National Institute for Health and Clinical Excellence were accessed. REVIEW METH-

ODS: The assessment of clinical effectiveness was based on a review of existing reviews plus an updated search for randomised controlled trials (RCTs). A decision tree with Monte Carlo simulation model was developed to assess the cost-effectiveness of BMT and MMT. Retention in treatment and opiate abuse parameters were sourced from the meta-analysis of RCTs directly comparing flexible MMT with flexible dose BMT. Utilities were derived from a panel representing a societal perspective. RESULTS: Most of the included systematic reviews and RCTs were of moderate to good quality, and focused on short-term (up to 1-year follow-up) outcomes of retention in treatment and the level of opiate use (self-report or urinalysis). Most studies employed a trial design that compared a fixed-dose strategy (i.e. all individuals received a standard dose) of MMT or BMT and were conducted in predominantly young men who fulfilled criteria as opiate-dependent or heroin-dependent users, without significant co-morbidities. RCT meta-analyses have shown that a fixed dose of MMT or BMT has superior levels of retention in treatment and opiate use than placebo or no treatment, with higher fixed doses being more effective than lower fixed doses. There was evidence, primarily from non-randomised observational studies, that fixed-dose MMT reduces mortality, HIV risk behaviour and levels of crime compared with no therapy and one small RCT has shown the level of mortality with fixed-dose BMT to be significantly less than with placebo. Flexible dosing (i.e. individualised doses) of MMT and BMT is more reflective of real-world practice. Retention in treatment was superior for flexible MMT than flexible BMT dosing but there was no significant difference in opiate use. Indirect comparison of data from population cross-sectional studies suggests that mortality with BMT may be lower than that with MMT. A pooled RCT analysis showed no significant difference in serious adverse events with MMT compared with BMT. Although treatment modifier evidence was limited, adjunct psychosocial and contingency interventions (e.g. financial incentives for opiate-free urine samples) appeared to enhance the effects of both MMT and BMT. Also, MMT and BMT appear to be similarly effective whether delivered in a primary care or outpatient clinic setting. Although most of the included economic evaluations were considered to be of high quality, none used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. One company (Schering-Plough) submitted cost-effectiveness evidence based on an economic model that had a 1-year time horizon and sourced data from a single RCT of flexible-dose MMT compared with flexible-dose BMT and utility values obtained from the literature; the results showed that for MMT vs no drug therapy, the incremental cost-effectiveness ratio (ICER) was pound 12,584/quality-adjusted life-year (QALY), for BMT versus no drug therapy, the ICER was pound 30,048/QALY and in a direct comparison, MMT was found to be slightly more effective and less costly than BMT. The assessment group model found for MMT versus no drug therapy that the ICER was pound 13,697/QALY, for BMT versus no drug therapy that the ICER was pound 26,429/QALY and, as with the industry model, in direct comparison, MMT was slightly more effective and less costly than BMT. When considering social costs, both MMT and BMT gave more health gain and were less costly than no drug treatment. These findings were robust to deterministic and probabilistic sensitivity analyses. CONCLUSIONS: Both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no

drug therapy in dependent opiate users. In direct comparison, a flexible dosing strategy with MMT was found be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT and therefore associated with a slightly higher health gain and lower costs. However, this needs to be balanced by the more recent experience of clinicians in the use of buprenorphine, the possible risk of higher mortality of MMT and individual opiate-dependent users' preferences. Future research should be directed towards the safety and effectiveness of MMT and BMT; potential safety concerns regarding methadone and buprenorphine, specifically mortality and key drug interactions; efficacy of substitution medications (in particular patient subgroups, such as within the criminal justice system, or within young people); and uncertainties in cost-effectiveness identified by current economic models. [References: 23]

9. Day E, Ison J, Strang J. Inpatient versus other settings for detoxification for opioid dependence. Cochrane Database of Systematic Reviews 2005;(2):CD004580.
Ref ID: 762
Abstract: BACKGROUND: There are a complex range of variables that can influence the course and subjective severity of opioid withdrawal. There is a growing evidence for the effectiveness of a range of medically-supported detoxification strategies, but little attention has been paid to the influence of the setting in which the process takes place. OBJECTIVES: To evaluate the effectiveness of any inpatient opioid detoxification programme when compared with all other time-limited detoxification programmes on the level of completion of detoxification, the intensity and duration of withdrawal symptoms, the nature and incidence of adverse effects, the level of engagement in further treatment post-detoxification, and the rates of relapse post-detoxification. SEARCH STRATEGY: Electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library Issue 2, 2008); MEDLINE (January 1966-May 2008); EMBASE (January 1988-May 2008); PsycInfo (January 1967-May 2008); CINAHL (January 1982-May 2008). In addition the Current Contents, Biological Abstracts, Science Citation Index and Social Sciences Index were searched. SELECTION CRITERIA: Randomised controlled clinical trials comparing inpatient opioid detoxification (any drug or psychosocial therapy) with other time-limited detoxification programmes (including residential units that are not staffed 24 hours per day, day-care facilities where the patient is not resident for 24 hours per day, and outpatient or ambulatory programmes, and using any drug or psychosocial therapy). DATA COLLECTION AND ANALYSIS: All abstracts were independently inspected by two reviewers (ED & JI) and relevant papers were retrieved and assessed for methodological quality using Cochrane Reviewers' Handbook criteria. MAIN RESULTS: Only one study met the inclusion criteria. This did not explicitly report the number of participants in each group that successfully completed the detoxification process, but the published data allowed us to deduce that 7 out of 10 (70%) in the inpatient detoxification group were opioid-free on discharge, compared with 11 out of 30 (37%) in the outpatient group. There was very limited data about the other outcomes of interest. AUTHORS' CONCLUSIONS: This review demonstrates that there is no good available research to guide the clinician about the outcomes or cost-effectiveness of inpatient or outpatient approaches to opioid detoxification. INPATIENT VERSUS OTHER

SETTINGS FOR DETOXIFICATION FOR OPIOID DEPENDENCE: Dependence on opioid drugs, such as heroin, morphine, and codeine, is a serious problem in many societies. Opioids are very difficult to quit using. The first step to quitting is detoxification, which can cause a number of painful symptoms as the drug withdraws from the body. Many people choose an inpatient detoxification program rather than trying to stop using opioids on their own. In an inpatient program, medications such as methadone can ease the symptoms of withdrawal and patients are in a secure, supportive environment with no access to opiates. However, inpatient programs are expensive and can disrupt patients' lives. An increasing number of outpatient programs are available, providing medication and some support while keeping the drug user in the community. In addition to drop-in programs, there are day centres and even residential facilities which are not staffed 24 hours, unlike inpatient programs. The authors of this review looked for research comparing inpatient and other types of opiate withdrawal programs to see which is more effective. They found only one study from 1975, which had 40 participants. The study suggested inpatient therapy might be more effective than outpatient therapy in the short-term, but all of the inpatients relapsed within three months after detoxification. Since they found only one outdated study which included very few patients, the Cochrane review authors could not conclude whether inpatient treatment is more effective than outpatient or other settings. More research must be done to measure the benefits and costs of inpatient detoxification, especially for more severely dependent users

10. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet 2005;44(7):661-80.
    Ref ID: 450
    Abstract: Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy, Papaver somniferum. The pharmacology of buprenorphine is unique in that it is a partial agonist at the opioid mu receptor. Buprenorphine undergoes extensive first-pass metabolism and therefore has very low oral bioavailability; however, its bioavailability sublingually is extensive enough to make this a feasible route of administration for the treatment of opioid dependence. The mean time to maximum plasma concentration following sublingual administration is variable, ranging from 40 minutes to 3.5 hours. Buprenorphine has a large volume of distribution and is highly protein bound (96%). It is extensively metabolised by N-dealkylation to norbuprenorphine primarily through cytochrome P450 (CYP) 3A4. The terminal elimination half-life of buprenorphine is long and there is considerable variation in reported values (mean values ranging from 3 to 44 hours). Most of a dose of buprenorphine is eliminated in the faeces, with approximately 10-30% excreted in urine. Naloxone has been added to a sublingual formulation of buprenorphine to reduce the abuse liability of the product. The presence of naloxone does not appear to influence the pharmacokinetics of buprenorphine. Buprenorphine crosses the placenta during pregnancy and also crosses into breast milk. Buprenorphine dosage does not need to be significantly adjusted in patients with renal impairment; however, since CYP3A activity may be decreased in patients with severe chronic liver disease, it is possible that the metabolism of buprenorphine will be altered in these patients. Although there is limited evidence in the literature to date,

drugs that are known to inhibit or induce CYP3A4 have the potential to diminish or enhance buprenorphine N-dealkylation. It appears that the interaction between buprenorphine and benzodiazepines is more likely to be a pharmacodynamic (additive or synergistic) than a pharmacokinetic interaction. The relationship between buprenorphine plasma concentration and response in the treatment of opioid dependence has not been well studied.The pharmacokinetic and pharmacodynamic properties of buprenorphine allow it to be a feasible option for substitution therapy in the treatment of opioid dependence. [References: 90]

11. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database of Systematic Reviews 2003;(3):CD002208.
    Ref ID: 772
    Abstract: BACKGROUND: Methadone maintenance treatment (MMT) is a long term opiod replacement therapy, effective in the management of opiod dependence. Even if MMT at high dosage is recommended for reducing illicit opioid use and promoting longer retention in treatment, at present day "the organisation and regulation of the methadone maintenance treatment varies widely". OBJECTIVES: To evaluate the efficacy of different dosages of MMT in modifying health and social outcomes and in promoting patients' familiar, occupational and relational functioning. SEARCH STRATEGY: We searched: - MEDLINE (OVID 1966-2001) - EMBASE (1988-2001) - ERIC (1988-2001) - Psychinfo (1947-2001) - Cochrane Controlled Trials Register (CCTR) (1947-2001) - Register of the Cochrane Drug and Alcohol Group (CDAG) (1947-2001) The CDAG search strategy was applied together with a specific MESH strategy.Further studies were searched through: · letters to the authors · check of references. SELECTION CRITERIA: Randomised Controlled Trials (RCT) and Controlled Prospective Studies (CPS) evaluating methadone maintenance at different dosages in the management of opioid dependence. Non-randomised trials were included when proper adjustment for confounding factors was performed at the analysis stage. DATA COLLECTION AND ANALYSIS: Data Extraction was performed separately by two reviewers. Discrepancies were resolved by a third reviewer. Quality assessments of the methodology of studies were carried out using CDAG checklist. MAIN RESULTS: 22 studies were excluded. 21 studies were included: 11 were RCTs (2279 participants) and 10 were CPSs (3715 participants).Outcomes: Retention rate - RCTs: High versus low doses at shorter follow-ups: RR=1.36 [1.13,1.63], and at longer ones: RR=1.62 [0.95,2.77]. Opioid use (self reported), times/w - RCTs: high versus low doses WMD= -2.00 [-4.77,0.77] high vs middle doses WMD= -1.89[-3.43, -0.35] Opioid abstinence, (urine based) at >3-4 w - RCTs: high versus low ones: RR=1.59 [1.16,2.18] high vs middle doses RR=1.51[0.63,3.61] Cocaine abstinence (urine based) at >3-4 w - RCTs: high versus low doses RR=1.81 [1.15,2.85] Overdose mortality - CPSs: high dose versus low dose at 6 years follow up: RR=0.29 [0.02-5.34] high dose vs middle dose at 6 years follow up: RR=0.38 [0.02-9.34] middle dose vs low dose at 6 years follow up: RR=0.57 [0.06-5.06] AUTHORS' CONCLUSIONS: Methadone dosages ranging from 60 to 100 mg/day are more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during

treatment. To find the optimal dose is a clinical ability, but clinician must consider these conclusions in treatment strategies. METHADONE MAINTENANCE AT DIFFERENT DOSAGES FOR OPIOID DEPENDENCE: People who are addicted to opioids have high risks of receiving an overdose of opioid, HIV, hepatitis B and C infections and criminal activity. This has led to a harm reduction treatment approach to drug addiction. Treatment is aimed at a reduction in these risks and relapses to opioid and polysubstance use and promoting psychosocial adjustment. Methadone maintenance treatment is a long-term opioid replacement therapy that is used to manage opioid dependence, reduce illicit opioid use and promote retention in treatment. Taken by mouth and active over 24 to 36 hours, it is an opioid drug that removes the euphoric effects of heroin and reduces withdrawal symptoms as well as being compatible with normal activities at work or school. The review authors identified 21 controlled trials involving a total of 5994 opioid users. In 11 of these trials, all from the USA, 2279 participants were randomised to methadone treatment at different doses or another treatment (buprenorphine or levomethadyl). Treatment was for between seven and 53 weeks. A further 10 controlled trials did not randomly assign the total of 3715 participants to a treatment. These were from various diverse countries and followed opioid users for one to 10 years. Higher doses of methadone (60 to 100 mg/day) were more effective than lower doses (1 to 39 mg/day) in retaining opioid users in therapy and in reducing illicit use of heroin and cocaine during treatment. Side effects of methadone appeared to be similar at the different doses, in one trial only. The organisation and regulation of methadone maintenance treatment varies widely and some countries have explicit guidelines for programme operation. Methadone maintenance treatment involves the prescription of a drug which itself causes dependence. This means that treatment is not naturally aimed at the total recovery of the individual

12. Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. Drug Alcohol Depend 2002;65(3):283-90.
    Ref ID: 582
    Abstract: The efficacy of methadone maintenance in opioid addiction was assessed in terms of programme retention rate and reduction of illicit opioid use by means of a meta-analysis of randomised, controlled and double blind clinical trials. The results were compared with interventions using buprenorphine and levo-acetylmethadol (LAAM). Trials were identified from the PubMed database from 1966 to December 1999 using the major medical subject headings 'methadone' and 'randomised controlled trial'. Data for a total of 1944 opioid-dependent patients from 13 studies were analysed. Sixty-four percent of patients received methadone, administered either as fixed or adjusted doses. Thus, 890 patients received > or = 50 mg/day (high dose group) and 392 were given < 50 mg/day (low dose group). Of 662 controls, 131 received placebo, 350 buprenorphine (265 at doses > or = 8 mg/day and 85 at doses < 8 mg/day) and 181 LAAM. High doses of methadone were more effective than low doses in the reduction of illicit opioid use (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.26--2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (< 8 mg/day) for retention

rates and illicit opioid use, but similar to high doses of buprenorphine (> or = 8 mg/day) for both parameters. Patients treated with LAAM had more risk of failure of retention than those receiving high doses of methadone (OR 1.92, 95% CI 1.32--2.78). It is proposed that in agonist-maintenance programmes, oral methadone at doses of 50 mg/day or higher is the drug of choice for opioid dependence

13. Fontaine E, Godfroid IO, Guillaume R. [Ultra-rapid detoxification of opiate dependent patients: review of the literature, critiques and proposition for an experimental protocol]. Encephale 2001;27(2):187-93.
    Ref ID: 596
    Abstract: Ultra-rapid opioid detoxification (UROD) is an increasingly popular technique for detoxifying patients addicted to opiates. This technique aims at reducing not only the duration but also the intensity of withdrawal by using general anesthesia coupled with a naloxone or naltrexone medication. In this paper the authors attempt to review the history of UROD and the logic of its procedure and results whilst also demonstrating its advantages and limits. METHOD: The MEDLINE database was searched from 1966 to 2000 using the terms "ultra-rapid opioid detoxification, rapid opioid detoxification under anesthesia, naloxone, naltrexone, opioid-related disorders". Additional data sources included bibliographies in textbooks on substance abuse. RESULTS: Nine studies identified in our search were analysed. The technique is based on a three-phases procedure. It consists of a medical and psychiatric selection of patients addicted to opiates, followed by the detoxification itself and finally a medical and psychosocial follow-up. A brief presentation is made of the theoretical aspects based on the use of a specific opioid receptor antagonist (naloxone and naltrexone). Only inpatients were included in the studies. The detoxification and anesthesia protocols varied. In every study all the subjects were completely detoxified. Only three studies included a control group and two used a randomized design. Three studies reported a follow-up beyond 30 days. DISCUSSION: Although this technique constitutes a safe and effective solution for opiate addicted patients, there are criticisms to be made. The absence of an animal model prior to the study of a human model, the lack of comparison with other procedures, the limitation of available literature, the cost and the risks of this technique and the lack of long-term treatment outcomes obtained from rigorous clinical trials, all call for further assessments. A more rigorous protocol based on the main areas of criticism is proposed (presentation of the inclusion and exclusion criterias, description of the three preliminary interviews, presentation of the UROD technique itself and finally a detailled nine month follow-up). CONCLUSION: Ultra-rapid opiate detoxification represents a potentially safe and effective treatment for opiate addicted patients but more rigorous research methods are needed to render this procedure entirely valid. [References: 26]

14. Gowing L, Ali R, White J. Opioid antagonists and adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2000;(2):CD002021.
    Ref ID: 628
    Abstract: BACKGROUND: Managed withdrawal, or detoxification, is not in itself a treatment for opioid dependence, but it is a required first step for many forms of longer-term

treatment. It may also represent the end point of an extensive period of treatment such as methadone maintenance. As such, managed withdrawal is an essential component of an effective treatment system. This review is one of a series that aims to assess the evidence as to the effectiveness of approaches to managing opioid withdrawal. OBJECTIVES: To assess the effectiveness of interventions involving the combined use of opioid antagonists an adrenergic agonists to manage the acute phase of opioid withdrawal. SEARCH STRATEGY: Multiple electronic databases, including Medline, Embase, Psychlit, Australian Medical Index and Current Contents, were searched using a strategy designed to retrieve references broadly addressing the management of opioid withdrawal. Reference lists of retrieved studies, reviews and conferences were handsearched. SELECTION CRITERIA: Studies that were included: involved administration of an opioid antagonist in combination with an alpha2 adrenergic agonist; had modification of the signs and symptoms of withdrawal as the aim of the intervention; involved participants who had been diagnosed as primarily opioid dependent and were undergoing clinically managed withdrawal; had as their primary focus the acute phase of withdrawal; reported detail of the type and dose of drugs used and the characteristics of study participants; reported information on the nature of withdrawal symptoms experienced, the occurrence of side effects OR rates of completion of withdrawal; and were randomized or quasi-randomized controlled clinical trials or prospective controlled cohort studies comparing the combination of opioid antagonists and adrenergic antagonists with another form of treatment. (The findings of prospective single group studies or case series, and controlled studies without a comparison treatment modality were considered in the narrative component of the review without being identified as included studies). DATA COLLECTION AND ANALYSIS: Potentially relevant studies were assessed for inclusion by one reviewer (LRG). Inclusion decisions were confirmed by consultation between all three reviewers. Included studies were assessed by all reviewers. One reviewer (LRG) undertook data extraction with the process confirmed by consultation between all three reviewers. Three studies compared treatment using an opioid antagonist-clonidine combination with treatment using clonidine only. This review incorporates data tables comparing maximum withdrawal scores and numbers of participants completing withdrawal for these three studies.. The capacity for data analysis is limited by differences in the assessment outcomes in the three studies and the likelihood of allocation bias in one study. Consequently, meta-analysis has not been undertaken to combine the findings of the three studies. MAIN RESULTS: Three studies (four reports) met the criteria for inclusi on in analytical components of this review. Six further studies were identified that managed withdrawal using opioid antagonists in combination with adrenergic agonists, but which did not meet the inclusion criteria (four were single group studies, 2 were controlled studies but did not include a comparison treatment modality). Findings of these studies are considered in narrative components of the review. Naltrexone was the primary opioid antagonist used to induce withdrawal. The most common approach was to administer naltrexone once a day, using an initial dose of 12.5mg, usually on day one or day two of treatment. Doses of clonidine were generally in the range of 01.-0.3mg three times a day. Five studies provided treatment on an outpatient basis, but all studies

provided extended care on the day naltrexone was first administered. (ABSTRACT TRUNCATED) [References: 4]

15. Gowing LR, Farrell M, Ali RL, White JM. Alpha-sub-2-adrenergic agonists in opioid withdrawal. Addiction 2002;97(1):49-58.
    Ref ID: 1061
    Abstract: RECORD STATUS: This article is based on a Cochrane Protocol/Review which is published in the Cochrane Database of Systematic Reviews where it will be regularly updated. Cochrane Reviews are of a high standard and are not evaluated by a CRD Reviewer. The citation is: Gowing L, Farrell M, Ali R, White JM. Alpha2 adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub2

16. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2009;(2):CD002024.
    Ref ID: 742
    Abstract: BACKGROUND: Withdrawal is a necessary step prior to drug-free treatment or as the end point of long-term substitution treatment. OBJECTIVES: To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists to manage opioid withdrawal. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2008), MEDLINE (January 1966-July 2008), EMBASE (January 1985-2008 Week 31), PsycINFO (1967 to 7 August 2008) and reference lists of articles. We also contacted manufacturers in the field. SELECTION CRITERIA: Controlled trials comparing alpha2-adrenergic agonists with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent. DATA COLLECTION AND ANALYSIS: One author assessed studies for inclusion and undertook data extraction. Inclusion decisions and the overall process were confirmed by consultation between all authors. MAIN RESULTS: Twenty-four studies, involving 1631 participants, were included. Twenty-one were randomised controlled trials.Thirteen studies compared a treatment regime based on an alpha2-adrenergic agonist with one based on reducing doses of methadone. Diversity in study design, assessment and reporting of outcomes limited the extent of quantitative analysis.Alpha2-adrenergic agonists are more effective than placebo in ameliorating withdrawal, and despite higher rates of adverse effects, are associated with significantly higher rates of completion of treatment.For the comparison of alpha2-adrenergic agonist regimes with reducing doses of methadone, there were insufficient data for statistical analysis, but withdrawal intensity appears similar to or marginally greater with alpha2-adrenergic agonists, while signs and symptoms of withdrawal occur and resolve earlier. Participants stay in treatment longer with methadone. No significant difference was detected in rates of completion of withdrawal with adrenergic agonists compared to reducing doses of methadone, or clonidine compared to lofexidine. Clonidine is associated with more adverse effects than reducing doses of methadone. Lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine AUTHORS' CONCLUSIONS: Clonidine and lofexidine are more effective than placebo

for the management of withdrawal from heroin or methadone. No significant difference in efficacy was detected for treatment regimes based on clonidine or lofexidine, and those based on reducing doses of methadone over a period of around 10 days but methadone is associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine. ALPHA2-ADRENERGIC AGONISTS FOR THE MANAGEMENT OF OPIOID WITHDRAWAL: Opioid withdrawal is similar with alpha2-adrenergic agonists and reducing doses of methadone but people stay in treatment longer with methadone and have fewer adverse effects. Managed withdrawal of opioids, or detoxification, is a required first step for longer-term treatments of opioid dependence. The signs and symptoms of opioid withdrawal usually begin 6 to 12 hours after the last dose of heroin or morphine and reach peak intensity within two to four days. Most physical withdrawal signs are no longer obvious after 7 to 14 days. The signs and symptoms develop 36 to 48 hours after the last dose of methadone. Suppression of withdrawal symptoms with methadone and gradual reduction of the methadone dose requires the use of a drug of dependence to treat opioid dependence and there are often governments restrictions on prescription of methadone. Consumers may also dislike of the protracted nature of methadone withdrawal. The alpha2-adrenergic agonist clonidine is used widely as a non-opioid alternative for managing opioid withdrawal. The review authors identified 24 controlled studies, involving 1631 participants who underwent managed withdrawal in 11 different countries. The review focused on alpha2-adrenergic agonists compared to placebo (four studies), reducing doses of methadone (14 studies), and lofexidine compared to clonidine (three studies). The alpha2-adrenergic agonists clonidine and lofexidine were more effective than placebo in managing withdrawal from heroin or methadone. Despite having adverse effects, they were associated with higher chances of completing treatment. Comparing reducing doses of methadone to clonidine or lofexidin for the management of withdrawal from opioids, withdrawal signs and symptoms were similar but occurred earlier with the alpha2-adrenergic agonists, within a few days of cessation of the opioid drugs. The chances of completing withdrawal were similar. People stayed in treatment longer with methadone regimes. Clonidine had more adverse effects (low blood pressure, dizziness, dry mouth, lack of energy) than reducing doses of methadone. Lofexidine had less effect on blood pressure than clonidine

17. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2009;(3):CD002025.
    Ref ID: 751
    Abstract: BACKGROUND: Managed withdrawal is a necessary step prior to drug-free treatment or as the end point of substitution treatment. OBJECTIVES: To assess the effectiveness of interventions involving the use of buprenorphine to manage opioid withdrawal, for withdrawal signs and symptoms, completion of withdrawal and adverse effects. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2008), MEDLINE (January 1966 to July 2008), EMBASE (January 1985 to 2008 Week 31), PsycINFO (1967 to 7 August 2008) and reference lists of articles. SELECTION CRITERIA: Randomised controlled trials of interventions involving the use of buprenorphine to modify the signs and symptoms of withdrawal

in participants who were primarily opioid dependent. Comparison interventions involved reducing doses of methadone, alpha2-adrenergic agonists, symptomatic medications or placebo, or different buprenorphine-based regimes. DATA COLLECTION AND ANALYSIS: One author assessed studies for inclusion and methodological quality, and undertook data extraction. Inclusion decisions and the overall process was confirmed by consultation between all authors. MAIN RESULTS: Twenty-two studies involving 1736 participants were included. The major comparisons were with methadone (5 studies) and clonidine or lofexidine (12 studies). Five studies compared different rates of buprenorphine dose reduction.Severity of withdrawal is similar for withdrawal managed with buprenorphine and withdrawal managed with methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. It appears that completion of withdrawal treatment may be more likely with buprenorphine relative to methadone (RR 1.18; 95% CI 0.93 to 1.49, P = 0.18) but more studies are required to confirm this.Relative to clonidine or lofexidine, buprenorphine is more effective in ameliorating the symptoms of withdrawal, patients treated with buprenorphine stay in treatment for longer (SMD 0.92, 95% CI 0.57 to 1.27, P < 0.001), and are more likely to complete withdrawal treatment (RR 1.64; 95% CI 1.31 to 2.06, P < 0.001). At the same time there is no significant difference in the incidence of adverse effects, but drop-out due to adverse effects may be more likely with clonidine. AUTHORS' CONCLUSIONS: Buprenorphine is more effective than clonidine or lofexidine for the management of opioid withdrawal. Buprenorphine may offer some advantages over methadone, at least in inpatient settings, in terms of quicker resolution of withdrawal symptoms and possibly slightly higher rates of completion of withdrawal. BUPRENORPHINE IS MORE EFFECTIVE THAN CLONIDINE OR LOFEXIDINE, AND MAY HAVE ADVANTAGES OVER METHADONE, FOR THE MANAGEMENT OF OPIOID WITHDRAWAL.: Dependence on opioid drugs (heroin, methadone) is a major health and social issue in many societies. Managed withdrawal from opioid dependence is an essential first step for drug-free treatment. This review of trials found that the drug buprenorphine is more effective than clonidine or lofexidine in reducing the signs and symptoms of opioid withdrawal, retaining patients in withdrawal treatment, and supporting the completion of treatment. There is no significant difference in the incidence of adverse effects, but patients treated with buprenorphine may be less likely to drop-out due to adverse effects than is the case with clonidine or lofexidine. There is limited evidence comparing buprenorphine with methadone, but it appears that completion of withdrawal may be more likely with buprenorphine and withdrawal symptoms may resolve more quickly with buprenorphine

18. Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database of Systematic Reviews 2006;(2):CD002022.
    Ref ID: 780
    Abstract: BACKGROUND: Withdrawal (detoxification) is necessary prior to drug-free treatment. It may also represent the end point of long-term opioid replacement treatment such as methadone maintenance. The availability of managed withdrawal is essential to an effective treatment system. OBJECTIVES: To assess the effectiveness of interventions involving the administration of opioid antagonists to induce opioid withdrawal with

concomitant heavy sedation or anaesthesia, in terms of withdrawal signs and symptoms, completion of treatment and adverse effects. SEARCH STRATEGY: We searched the Drugs and Alcohol Group register (October 2003), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2004), Medline (January 1966 to January 2005), Embase (January 1985 to January 2005), PsycINFO (1967 to January 2005), and Cinahl (1982 to December 2004) and reference lists of studies. SELECTION CRITERIA: Controlled trials comparing antagonist-induced withdrawal under heavy sedation or anaesthesia with another form of treatment, or a different regime of anaesthesia-based antagonist-induced withdrawal. DATA COLLECTION AND ANALYSIS: One reviewer assessed studies for inclusion and undertook data extraction and assessed quality. Inclusion decisions and the overall process were confirmed by consultation between all three reviewers. MAIN RESULTS: Six studies (five randomised controlled trials) involving 834 participants met the inclusion criteria for the review.Antagonist-induced withdrawal is more intense but less prolonged than withdrawal managed with reducing doses of methadone, and doses of naltrexone sufficient for blockade of opioid effects can be established significantly more quickly with antagonist-induced withdrawal than withdrawal managed with clonidine and symptomatic medications. The level of sedation does not affect the intensity and duration of withdrawal, although the duration of anaesthesia may influence withdrawal severity. There is a significantly greater risk of adverse events with heavy, compared to light, sedation (RR 3.21, 95% CI 1.13 to 9.12, P = 0.03) and probably also other forms of detoxification. AUTHORS' CONCLUSIONS: Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported. The high cost of anaesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued. THE POTENTIAL RISKS AND HIGH COST OF USING OPIOID BLOCKING DRUGS DURING HEAVY SEDATION OR ANAESTHESIA TO BRING ON WITHDRAWAL OUTWEIGH THE BENEFITS: Drugs that block opioids are sometimes given to opioid dependent people while they are under heavy sedation or anaesthesia to speed up withdrawal. The review of trials shows that this sort of withdrawal treatment is quicker than withdrawal managed with reducing doses of methadone or clonidine plus symptomatic medications. The intensity of withdrawal experienced with anaesthesia-based approaches is similar to that experienced with similar approaches using only minimal sedation, but there is a significantly increased risk of serious adverse events with anaesthesia-assisted approaches. The lack of additional benefit, and increased risk of harm, suggest that this form of treatment should not be pursued

19. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database of Systematic Reviews 2006;(1):CD002021.
    Ref ID: 781
    Abstract: BACKGROUND: Managed withdrawal is necessary prior to drug-free treatment. It may also represent the end point of long-term opioid replacement treatment.

OBJECTIVES: To assess the effectiveness of opioid antagonists in combination with minimal sedation to induce withdrawal, in terms of intensity of withdrawal, adverse effects and completion of treatment. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2005, which includes the Cochrane Drugs and Alcohol Group register), MEDLINE (January 1966 to August 2005), EMBASE (January 1985 to August 2005), PsycINFO (1967 to August 2005), and CINAHL (1982 to July 2005) and reference lists of articles. SELECTION CRITERIA: Experimental interventions involved the use of opioid antagonists in combination with minimal sedation to manage withdrawal in opioid-dependent participants compared with other approaches or different opioid antagonist regime. DATA COLLECTION AND ANALYSIS: One reviewer assessed studies for inclusion and undertook data extraction and trial quality. Study authors were contacted for additional information. MAIN RESULTS: Nine studies (5 randomised controlled trials), involving 775 participants, met the inclusion criteria for the review.Withdrawal induced by opioid antagonists in combination with an adrenergic agonist is more intense than withdrawal managed with clonidine or lofexidine alone, but the overall severity is less. Limited data showed that antagonist-induced withdrawal may be more severe when the last opioid used was methadone rather than heroin or another short-acting opioid. Delirium may occur following the first dose of opioid antagonist, particularly with higher doses (> 25mg naltrexone).The studies included suggest there is no significant difference in rates of completion of treatment for withdrawal induced by opioid antagonists, in combination with an adrenergic agonist, compared with adrenergic agonist alone. AUTHORS' CONCLUSIONS: The use of opioid antagonists combined with alpha2 adrenergic agonists is a feasible approach to the management of opioid withdrawal. However, it is unclear whether this approach reduces the duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with an adrenergic agonist.A high level of monitoring and support is desirable for several hours following administration of opioid antagonists because of the possibility of vomiting, diarrhoea and delirium.Further research is required to confirm the relative effectiveness of antagonist-induced regimes, as well as variables influencing the severity of withdrawal, adverse effects, the most effective antagonist-based treatment regime, and approaches that might increase retention in subsequent naltrexone maintenance treatment. OPIOID ANTAGONISTS WITH MINIMAL SEDATION FOR OPIOID WITHDRAWAL: Opioid antagonists induce withdrawal by displacing opioids from their receptors. Adrenergic agonists, acting through non-opioid mechanisms, can reduce withdrawal symptoms induced by antagonists. Withdrawal induced by the combination of these substances is more intense early in treatment, but overall severity is less, no difference for completion of treatment

20. Griffith JD, Rowan-Szal GA, Roark RR, Simpson DD. Contingency management in outpatient methadone treatment: a meta-analysis. Drug Alcohol Depend 2000;58(1-2):55-66.
    Ref ID: 633
    Abstract: A meta-analysis was conducted on contingency management interventions in

outpatient methadone treatment settings. The outcome measure of interest was drug use during treatment, as detected through urinalysis. The results confirm that contingency management is effective in reducing supplemental drug use for these patients. The analysis of behavioral interventions yielded an overall effect size (r) of 0.25 based on 30 studies. Significant moderators of outcomes included type of reinforcement provided, time to reinforcement delivery, the drug targeted for behavioral change, number of urine specimens collected per week, and type of subject assignment. These factors represent important considerations for reducing drug use during treatment

21. Helm S, Trescot AM, Colson J, Sehgal N, Silverman S. Opioid antagonists, partial agonists, and agonists/antagonists: the role of office-based detoxification. Pain Physician 2008;11(2):225-35.
    Ref ID: 335
    Abstract: BACKGROUND: The opioid receptor antagonists naloxone and naltrexone are competitive antagonists at the mu, kappa, and sigma receptors with a higher affinity for the mu receptor and lacking any mu receptor efficacy. Buprenorphine is classified as a partial agonist. It has a high affinity, but low efficacy at the mu receptor where it yields a partial effect upon binding. It also, however, possesses kappa receptor antagonist activity making it useful not only as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies. Naloxone is added to sublingual buprenorphine (Suboxone) to prevent the intravenous abuse of buprenorphine. The same product (sublingual buprenorphine) when used alone (i.e. without naloxone) is marketed as Subutex. OBJECTIVE: To evaluate and update the available evidence regarding the use of agonist/antagonists to provide office-based opioid treatment for addiction. METHODS: A review using databases of EMBASE and MEDLINE (1992 to December 2007). These included systematic reviews, narrative reviews, prospective and retrospective studies, as well as cross-references from other articles. OUTCOME MEASURES: The primary outcome measure was treatment retention. Other outcome measures included opioid-free urine drug testing, opioid craving, intensity of withdrawal, pain reduction, adverse effects, addiction severity index, and HIV risk behavior. RESULTS: The results found 17 studies, 1 systematic review, 12 RCTs, and 4 observational series, which document the efficacy and safety of buprenorphine alone and in combination with naloxone in detoxifying and maintaining abstinence from illicit drugs in patients with opioid addiction. CONCLUSION: Based on the present evaluation, it appears that opioid antagonists, partial agonists, and antagonists are useful in office-based opioid treatment for addiction. [References: 21]

22. Horspool MJ, Seivewright N, Armitage CJ, Mathers N. Post-treatment outcomes of buprenorphine detoxification in community settings: a systematic review. Eur Addict Res 2008;14(4):179-85.
    Ref ID: 294
    Abstract: A systematic review was undertaken to examine studies of buprenorphine detoxification that has included post-treatment outcomes as well as more immediate aspects of progress. Studies were required to report details of buprenorphine withdrawal regime and post-treatment outcomes including abstinence rates. Only five studies met these criteria, with buprenorphine regimes lasting 3 days to several weeks, and with

variable follow-up. Detoxification completion rates were 65-100%, but relatively few treatment completers were then drug free at their follow-up appointments. In subsequent prescribing, more patients had returned to opioid maintenance than complied with naltrexone. Our preliminary review indicates that buprenorphine is a suitable medication for the process of opiate detoxification but that this newer treatment option has not led to higher rates of abstinence following withdrawal. Further studies are required to more substantially examine abstinence outcomes, as well as characteristics which predict success. Copyright (c) 2008 S. Karger AG, Basel. [References: 28]

23. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. Addiction 2006;101(4):491-503.
Ref ID: 419
Abstract: AIMS: To determine the efficacy of naltrexone in reducing illicit opioid use and the potential moderating role of treatment retention. DESIGN: First, randomized controlled trials (RCTs) comparing the regimens of treatment using the opioid antagonist, naltrexone, with controls were analysed by meta-analysis for treatment effect with regard to a range of outcome criteria. The degree of heterogeneity was also determined. The moderating effect of other interventions during naltrexone maintenance was then estimated, particularly with regard to their effect on treatment retention. PARTICIPANTS: Fifteen studies involving 1,071 patients were found. MEASUREMENTS: All available outcomes were analysed in 10 studies of naltrexone versus control (seven placebo) and six studies of randomized psychosocial/psychopharmacological interventions. FINDINGS: Significant heterogeneity was found in the efficacy of naltrexone. Level of retention in treatment was found to be a moderator, explaining most of the heterogeneity found. Overall, naltrexone was significantly better than control conditions in reducing the number of opioid-positive urines. This effect was only present in the high retention subgroup for differences in retention. Contingency management (CM) increased retention and naltrexone use, resulting in a reduced number of opioid-positive urines. CONCLUSION: Retention is important to the effect of naltrexone in treating opioid dependence. Contingency management is a promising method of increasing retention. [References: 42]

24. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with methadone for opioid dependence: a meta-analytical study. Nordic Journal of Psychiatry 2007;61(4):288-95.
Ref ID: 358
Abstract: The two aims of this study were to analyse the impact of methadone on outcome, and to confirm the results from previous meta-analyses by using a different methodology. The literature on randomized controlled trials (RCT) of methadone as maintenance treatment for opioid dependence was systematically reviewed. Eight studies involving 1511 patients were included. Both dichotomous and continuous variables were transformed into the standardized effect size (d). Homogeneity was analysed. A random effect model was used in all calculations. The combined analyses for retention, abuse and criminality were all significant: d=0.90, d=0.61, and d=0.35, respectively. A test of heterogeneity was significant for all three outcomes: P<0.01 for all comparisons. The

type of study design was a significant moderator in five of nine comparisons: for retention in all three comparisons, concerning abuse in gradual detoxification vs. untreated controls and concerning criminality in placebo vs. untreated controls. In these subgroups, three of six studies were homogeneous. In one study, methadone maintenance treatment reduced abuse of illegal opioids in prisoners. We conclude that methadone maintenance treatment in opioid dependence shows positive effects on retention, opioid abuse and criminality compared with non-active controlled conditions. Type of study design could explain some of the heterogeneity found. A different meta-analytical approach made it possible to confirm effects of methadone on retention and opioid abuse from previous studies and document effect on criminality

25. Jordan JB. Acupuncture treatment for opiate addiction: a systematic review. J Subst Abuse Treat 2006;30(4):309-14.
    Ref ID: 407
    Abstract: A review of the efficacy of acupuncture as treatment for opiate addiction, covering 33 years of reported literature in western scientific journals, was systematically undertaken. Some abstracts from Chinese language journals were also briefly reviewed. Supportive evidence often came from non-controlled nonblinded methodologies. When well-designed clinical trials (randomized, controlled, single-blind methodologies) were used, there was no significant evidence for acupuncture being a more effective treatment than controls. Some of the current supportive evidence for efficacy came from Chinese journals that have not been translated into English yet. [References: 60]

26. Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids: study of chronic pain patients. Can Fam Physician 2006;52(9):1081-7.
    Ref ID: 384
    Abstract: OBJECTIVE: To review the evidence on identifying and managing misuse of and dependence on opioids among primary care patients with chronic pain. QUALITY OF EVIDENCE: MEDLINE was searched using such terms as "opioid misuse" and "addiction." The few studies on the prevalence of opioid dependence in primary care populations were based on retrospective chart reviews (level II evidence). Most recommendations regarding identification and management of opioid misuse in primary care are based on expert opinion (level III evidence). MAIN MESSAGE: Physicians should ask all patients receiving opioid therapy about current, past, and family history of addiction. Physicians should take "universal precautions" that include careful prescribing and ongoing vigilance for signs of misuse. Patients suspected of opioid misuse can be treated with a time-limited trial of structured opioid therapy if they are not acquiring opioids from other sources. The trial should consist of daily to weekly dispensing, regular urine testing, and tapering of doses of opioids. If the trial fails or is not indicated, patients should be referred for methadone or buprenorphine treatment. CONCLUSION: Misuse of and dependence on opioids can be identified and managed successfully in primary care. [References: 49]

27. Kornor H, Waal H. From opioid maintenance to abstinence: a literature review. Drug and Alcohol Review 2005;24(3):267-74.

Ref ID: 935
Abstract: RECORD STATUS: This record is a structured abstract written by CRD reviewers. The original has met a set of quality criteria. Since September 1996 abstracts have been sent to authors for comment. Additional factual information is incorporated into the record. Noted as [A:....]
AUTHOR'S OBJECTIVES: To estimate the extent of opioid abstinence from former maintenance patients; to determine patient and treatment factors related to abstinence rates; and to assess the need for research
STUDY SELECTION - SPECIFIC INTERVENTIONS: Studies of treatment that was time-limited or had no pre-set time limit, or of abstinence-based policies, were eligible for inclusion. The mean duration of methadone treatment was 22.2 months (range: 1.0 to 48.1). Studies of detoxification per se, defined as programmes of less than 30 days' duration, were excluded. The included studies comprised therapeutic detoxification programmes (for methadone patients considered treatment completers according to study-defined criteria and who choose to detoxify) or non-therapeutic detoxification programmes (all other reasons for ending methadone treatment); some programmes used flexible detoxification regimens. Some of the included studies also involved psychosocial services
STUDY SELECTION - PARTICIPANTS: Studies of participants aged 18 years or older were eligible for inclusion. Most studies evaluated participants selected from methadone maintenance programmes; others were performed in general practice or in young heroin addicts. The majority of the participants were male and the mean age was 30 years (range: 19 to 35.6). The included participants had been regularly dependent on illicit opioids for an average of 7.4 months
STUDY SELECTION - OUTCOMES: Studies that reported post-treatment abstinence rates were eligible for inclusion. Definitions of abstinence varied according to the substance used, frequency of use and time. Most of the included studies assessed abstinence using urine samples, clinical records, official records and interviews at follow-up
STUDY SELECTION - STUDY DESIGNS: All study designs were eligible for inclusion
SEARCHING: MEDLINE (including PREMEDLINE) and PsycINFO (1966 to 2003) were searched using the reported search terms. The reference lists of key articles, including relevant review articles and textbooks, were also screened. Non-English language articles were excluded
VALIDITY ASSESSMENT: The authors did not state that they assessed validity
STUDY SELECTION - HOW WERE DECISIONS ON THE RELEVANCE OF PRIMARY STUDIES MADE?: Two reviewers independently determined the eligibility of the studies
DATA EXTRACTION: The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Abstinence rates, in addition to any treatment and patient characteristics reported to be related to abstinence rates, were extracted from each included study
METHODS OF SYNTHESIS - HOW WERE THE STUDIES COMBINED?: A pooled abstinence rate was obtained for all studies combined, and separately for those that addressed therapeutic or non-therapeutic detoxification. Results of relationships between patient and treatment characteristics were reported as positively or negatively related, or

unrelated
METHODS OF SYNTHESIS - HOW WERE DIFFERENCES BETWEEN STUDIES INVESTIGATED?: The influence of treatment and patient characteristics on abstinence rate was investigated (as detailed above)
RESULTS OF THE REVIEW: Twelve studies (n=9,718) met the inclusion criteria. The designs of these studies were not clear, although the authors reported that studies were mostly naturalistic follow-up studies. Two of the studies appeared to be randomised controlled trials. The duration of follow-up ranged from 1 month to 103.2 months. Overall, 33% of patients in the included studies were abstinent (or had a period of abstinence) from at least opioids for an average of 2 years following detoxification. The rates of abstinence ranged from 22 to 86%. Treatment characteristics. The abstinence rates were higher in patients who volunteered to participate in detoxification programmes compared with those whose participation was based on staff recommendation (47% versus 23%). Methadone maintenance dose and psychosocial support were not related to abstinence rate. Patient characteristics. Inconsistencies were reported in the relationship between patient characteristics and abstinence rates. Age, ethnicity and educational level were all shown to have a positive relationship with abstinence rate in some studies, but not others. Similarly, duration or severity of dependence, detoxification difficulties, social problems and criminal behaviour were shown to have a negative relationship in some studies, but not others
AUTHOR'S CONCLUSION: Abstinence-orientated maintenance therapy may be suitable for a subgroup of patients, but there is a substantial need for a research update
CRD COMMENTARY: The review question was broadly defined in terms of the population, intervention and outcomes; no restrictions were applied to study design. The search strategy was not comprehensive and it was unclear whether methods were used to minimise publication bias. Furthermore, 22 non-English language articles were excluded at the search stage. Methods were used to minimise bias when selecting studies for inclusion, although it was unclear if methods to minimise reviewer error and bias were used in the data extraction process. The validity of the included studies was not assessed, thus it is not possible to comment on the reliability of the results. Details presented on each of the included studies were limited, but highlighted considerable clinical and methodological variations. The authors did not report the study designs, and only 20% of those included in the study populations were reported in the results; the reason for this is not clear. The authors acknowledged this issue of selection bias and stated that the included studies provide no basis for generalisation. Results presented on prognostic factors were inconsistent and several studies did not report the statistical methods used to determine a relationship with abstinence rates; this suggests the need for cautious interpretation. Furthermore, many of the included studies were published some 20 to 30 years ago, suggesting that relevance to current practice is unlikely. Given the considerable differences across the included studies, the decision to combine the abstinence rates was not appropriate. Based on the limitations of this review, both in the evidence presented and review methodology, considerable caution is needed in the interpretation of the included studies and the authors' conclusion. However, it would appear that the call for further research is supported

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Practice: The authors stated that if the review had any implications for practice the following would be recommended. Patients should not be detoxified against their will or too early; patients in indefinite maintenance who achieve sufficient stabilisation should be able to make an informed decision on continuation or discontinuation of treatment; and time-limited treatment programmes may be an option for suitably chosen patients. Research: The authors stated that there is a void in the research on buprenorphine. A comparison of the long-term outcomes of discontinued methadone and buprenorphine is needed. Comparisons between less and more severely opioid-dependent patients are also needed

28. Kunz S, Schulz M, Syrbe G, Driessen M. Acupuncture of the ear as therapeutic approach in the treatment of alcohol and substance abuse - A systematic review. Sucht 2004;50(3):196-203.
    Ref ID: 180
    Abstract: Aims: Acupuncture as a treatment of substance-related disorders has reached increasing acceptance. A systematic review of the available studies is provided to determine, if this trend is supported by the scientific evidence from RCT's. Methodology: A systematic literature search and critical appraisal of the studies was done. Results: Fourteen randomised controlled studies (RCT) of ear acupuncture in the treatment of withdrawal from opiate-, cocaine- or alcohol-dependent patients were identified. A meta-analysis of the studies based on effect size could not be performed because of varying objectives, methods, sample characteristics and different dropout rates. Conclusion: The available scientific evidence does not support the efficacy of acupuncture in the treatment of withdrawal in opiate-, cocaine- and alcohol-dependent patients

29. Layson-Wolf C, Goode JV, Small RE. Clinical use of methadone. Journal of Pain and Palliative Care Pharmacotherapy 2002;16(1):29-59.
    Ref ID: 548
    Abstract: Methadone hydrochloride is a mu-opioid agonist that has been used for the treatment of pain and for the management and maintenance of opioid withdrawal for over 50 years. Several characteristics make methadone a useful drug. However, these same characteristics and wide interpatient variability can make methadone difficult to use safely. A MEDLINE search was conducted on publications between January 1996 and May 2001 to identify literature relevant to this subject. Those publications were reviewed, and from them, other literature was identified and reviewed. Published studies demonstrate methadone's efficacy in pain management and in opioid withdrawal. However, interpatient variability in pharmacokinetic variables of methadone produces difficulties in developing guidelines for methadone use. Clinicians should not be deterred from use of this drug which has been shown to benefit patients in both pain management and methadone maintenance, but an individualized patient approach must be taken to use methadone safely. [References: 95]

30. Liu T-T, Shi J, Epstein DH, Bao Y-P, Lu L. A meta-analysis of acupuncture combined with opioid receptor agonists for treatment of opiate-withdrawal symptoms. Cell Mol Neurobiol 2009;29(4):449-54.

Ref ID: 23

Abstract: This review extends a prior meta-analysis of acupuncture's utility for treating opioid detoxification, addressing the efficacy of acupuncture when combined with allopathic therapies. Both English and Chinese databases were searched for randomized trials comparing acupuncture combined with opioid agonist treatment versus opioid agonists alone for treating symptoms of opioid withdrawal. The methodological quality of each study was assessed with Jadad's scale (1-2 = low; 3-5 = high). Meta-analysis was performed with fixed- or random-effect models in RevMan software; the outcome measures assessed were withdrawal-symptoms score, relapse rate, side effects, and medication dosage. Withdrawal-symptom scores were lower in combined treatment trials than in agonist-alone trials on withdrawal days 1, 7, 9, and 10. Combined treatment also produced lower reported rates of side effects and appeared to lower the required dose of opioid agonist. There was no significant difference on relapse rate after 6 months. This meta-analysis suggests that acupuncture combined with opioid agonists can effectively be used to manage the withdrawal symptoms. One limitation of this meta-analysis is the poor quality of the methodology of some included trials. High-quality studies are needed to confirm findings regarding the side effects and medication dosage. copyright 2008 Springer Science+Business Media, LLC

31. Mattick RP, Kimber J, Breen Court, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2008;(2):CD002207.

    Ref ID: 752

    Abstract: BACKGROUND: Buprenorphine has been reported as an alternative to methadone for maintenance treatment of opioid dependence, but differing results are reported concerning its relative effectiveness indicating the need for an integrative review. OBJECTIVES: To evaluate the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use. SEARCH STRATEGY: We searched the following databases up to October 2006: Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Current Contents, Psychlit, CORK , Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress databases, reference lists of identified studies and reviews, authors were asked about any other published or unpublished relevant RCT. SELECTION CRITERIA: Randomised clinical trials of buprenorphine maintenance versus placebo or methadone maintenance. DATA COLLECTION AND ANALYSIS: Authors separately and independently evaluated the papers and extracted data for meta-analysis. MAIN RESULTS: Twenty four studies met the inclusion criteria (4497 participants), all were randomised clinical trials, all but six were double-blind. The method of allocation concealment was not clearly described in the majority (20) of the studies, but where it was reported the methodological quality was good. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR=1.50; 95% CI: 1.19 - 1.88), medium (RR=1.74; 95% CI: 1.06 - 2.87), and high doses (RR=1.74; 95% CI: 1.02 - 2.96). The high statisitical heterogenity prevented

the calculation of a cumulative estimate. However, only medium and high dose buprenorphine suppressed heroin use significantly above placebo. Buprenorphine given in flexible doses was statistically significantly less effective than methadone in retaining patients in treatment (RR= 0.80; 95% CI: 0.68 - 0.95), but no different in suppression of opioid use for those who remained in treatment. Low dose methadone is more likely to retain patients than low dose buprenorphine (RR= 0.67; 95% CI: 0.52 - 0.87). Medium dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for medium dose buprenorphine over medium dose methadone in retention (RR=0.79; 95% CI:0.64 - 0.99) and medium dose buprenorphine was inferior in suppression of heroin use. AUTHORS' CONCLUSIONS: Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than methadone delivererd at adequate dosages. BUPRENORPHINE MAINTENANCE VERSUS PLACEBO OR METHADONE MAINTENANCE FOR OPIOID DEPENDENCE: Buprenorphine can reduce heroin use compared with placebo, although it is less effective than methadone. Methadone is widely used as a replacement for heroin in medically-supported maintenance or detoxification programs. Two other drugs are sometimes used to try and help lower use of heroin, specifically buprenorphine and LAAM (levo-alpha-acetylmethadol). Buprenorphine is an opioid drug that is not as powerful as heroin and methadone, although the effects of buprenorphine may last longer. Buprenorphine can be taken once every two days. The review of trials found that buprenorphine at medium (8mg -15mg) and high doses (16mg) can reduce heroin use effectively compared with placebo, although it is less effective than methadone, especially if methadone is prescribed at adequate dose levels of between 60mg and 120mg per day

32. Mayet S, Farrell M, Ferri Marica MF, Amato L, Davoli M. Psychosocial treatment for opiate abuse and dependence. Cochrane Database of Systematic Reviews 2004;(4):CD004330.
    Ref ID: 791
    Abstract: BACKGROUND: Substance dependence is a social and public health problem; therefore it is a priority to develop effective treatments. Previous Cochrane reviews have explored the efficacy of pharmacotherapy for opiate dependence. This current review focuses on the role of psychosocial interventions alone for the treatment of opiate dependence. There is some evidence for the effectiveness of psychosocial interventions, but no systematic review has even been carried out. OBJECTIVES: To assess the efficacy and acceptability of psychosocial interventions alone for treating opiate use disorders. SEARCH STRATEGY: Electronic searches of databases: Cochrane drugs and Alcohol Group Register of Trials (21 January 2004); Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, Issue 1, 2004); MEDLINE (1966-2003), LILACS (1982-2003), EMBASE (1980-2003), PsycINFO (1872-2003). In addition reference searching, personal communication, conference abstracts, unpublished trials, book chapters on treatment of opioid dependence. SELECTION CRITERIA: Randomised controlled trials comparing psychosocial interventions alone versus pharmacological interventions or placebo or non-intervention for treating opioid use disorders. DATA COL-

LECTION AND ANALYSIS: Two reviewers independently assessed trial quality and extracted data. MAIN RESULTS: Five trials involving 389 participants were included. These analysed Contingency Management, Brief Reinforcement Based Intensive Outpatient Therapy coupled with Contingency Management, Cue Exposure therapy, Alternative Program for Methadone Maintenance Treatment Program Drop-outs (MMTP) and Enhanced Outreach-Counselling Program. All the treatments were studied against the control (standard) treatment; therefore it was not possible to identify which type of psychosocial therapy was most effective.The main findings were that both Enhanced Outreach Counselling and Brief Reinforcement Based Intensive Outpatient Therapy coupled with Contingency Management had significantly better outcomes than standard therapy regarding relapse to opioid use, re-enrolment in treatment and retention in treatment. At 1-month and 3- month follow up the effects of Reinforcement Based Intensive Outpatient Therapy were not sustained. There was no further follow up of the Enhanced Outreach Counselling group. The Alternative Program for MMTP Drop-outs and the behavioural therapies of Cue Exposure and Contingency Management alone were no better than the control. As the studies were heterogeneous, it was not possible to pool the results and perform a meta-analysis. AUTHORS' CONCLUSIONS: The available evidence has low numbers and is heterogeneous. At present psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment. It is important to develop a better evidence base for psychosocial interventions to assist in future rationale planning of opioid use drug treatment services. CURRENTLY THERE IS NOT ENOUGH EVIDENCE TO CONCLUDE THAT PSYCHOSOCIAL TREATMENTS ALONE ARE ADEQUATE TO TREAT PEOPLE WITH OPIATE ABUSE AND DEPENDENCE.: Psychosocial interventions alone are offered to people with opiate use disorders indiscriminately across countries; sometimes representing the most prevalent treatment after substitution therapy. Despite its wide use in clinical practice, no systematic review of effectiveness has ever been carried out. This review demonstrated that there was inadequate evidence available to prove the effectiveness of psychosocial interventions alone for the treatment of opiate dependence or that they are superior to any other type of treatment

33. Minozzi Silvia AU: Amato Laura AU: Davoli Marina. Maintenance treatments for opiate dependent adolescent. Cochrane Database of Systematic Reviews: Reviews 2009;Issue 2

    Ref ID: 1071

    Abstract: RECORD STATUS: This is a regularly updated Cochrane review. Please see the Cochrane Library for the full version

    AUTHOR'S OBJECTIVES: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on retaining adolescents in treatment, reducing the use of substances and reducing health and social status The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless no studies have been published

which systematically assess the effectiveness of the pharmacological maintenance treatment among adolescent
SEARCHING: We searched the Cochrane Drugs and Alcohol Group's trials register (august 2008), MEDLINE (January 1966 to august 2008), EMBASE (January 1980 to august 2008), CINHAL (January 1982 to august 2008) and reference lists of articles
VALIDITY ASSESSMENT: Randomised and controlled clinical trials comparing any maintenance pharmacological interventions alone or associated with psychosocial intervention with no intervention, placebo, other pharmacological intervention included pharmacological detoxification or psychosocial intervention in adolescent (13-18 years)
DATA EXTRACTION: Two reviewers independently assessed trial quality and extracted data
RESULTS OF THE REVIEW: Two trials involving 187participants were included. One study compared methadone with LAAM for maintenance treatment lasting16 weeks after which patients were detoxified, the other compared maintenance treatment with buprenorphine - naloxone with detoxification with buprenorphine. No meta-analysis has been performed because the two studies assessed different comparisons. Maintenance treatment seems more efficacious in retaining patients in treatment but not in reducing patients with positive urine at the end of the study. Self reported opioid use at 1 year follow up was significantly lower in the maintenance group even if both group reported high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment at 12 month follow up
AUTHOR'S CONCLUSION: It is difficult to draft conclusions on the basis of only two trials. One of the possible reason for the lack of evidence could be the difficulty to conduct trial with young people due to practical and ethic reasons. MAINTENANCE TREATMENTS FOR OPIATE DEPENDENT ADOLESCENTS: It is difficult to draw conclusions about the use of maintenance pharmacological interventions from only two trials. Substance abuse among adolescents (13 to 18 years old) is a serious and growing problem. The most common drugs used by young people worldwide are cannabis and inhalants. Psychostimulants (ecstasy and amphetamines), cocaine, LSD, heroin and other opioids are also used. Many adolescents who use heroin start by snorting it but some progress to injection. Heroin is used sporadically by the majority who use it, but it can become an addictive disorder. In adults, pharmacotherapy is a necessary and acceptable part of effective treatment for opioid dependence. Among adolescents, medications have been used infrequently and a choice has to be made between detoxification and maintenance treatment. The review authors searched the literature and identified two controlled trials from the USA that involved 187 heroin addicts, aged 14 to 21 years; the participants were treated as outpatients. One study of 37 participants compared methadone with LAAM for maintenance treatment. After 16 weeks of maintenance treatment the adolescents were detoxified. The two maintenance treatments gave similar improvements in social functioning. No side effects were reported. The second trial of 150 adolescents compared buprenorphine and naloxone as maintenance treatment with buprenorphine detoxification over 14 days. The maintenance treatment for nine weeks followed by tapered doses up to 12 weeks seemed to be more effective in retaining patients in treatment but not in reducing the use of drugs of abuse. At one -year follow up, self-reported

opioid use was clearly less in the maintenance group and more adolescents were enrolled in other addiction programs. The most common side effect in both groups was headache. No participants left the study because of side effects. Conducting trials with young people may be difficult for both practical and ethical reasons

34. Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. Cochrane Database of Systematic Reviews 2009;(2):CD006749.
Ref ID: 757
Abstract: BACKGROUND: The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless no studies have been published which systematically assess the effectiveness of the pharmacological detoxification among adolescents. OBJECTIVES: To assess the effectiveness of any detoxification treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on completion of treatment, reducing the use of substances and improving health and social status. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (August 2008), MEDLINE (January 1966 to August 2008), EMBASE (January 1980 to August 2008), CINHAL (January 1982 to August) and reference lists of articles. SELECTION CRITERIA: Randomised and controlled clinical trials comparing any pharmacological interventions alone or associated with psychosocial intervention aimed at detoxification with no intervention, placebo, other pharmacological intervention or psychosocial intervention in adolescents (13-18 years). DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed trial quality and extracted data. MAIN RESULTS: One trial involving 36 participants was included. It compares buprenorphine with clonidine for detoxification. No difference was found for drop out: RR 0.45 (95%CI: 0.20 - 1.04) and acceptability of treatment: withdrawal score WMD: 3.97 (95%CI -1.38, 9.32). More participants in the buprenorphine group initiated naltrexone treatment: RR 11.00 [95%CI 1.58, 76.55]. AUTHORS' CONCLUSIONS: It is difficult to draft conclusions on the basis of only one trial with few participants. Furthermore, the only study included did not consider the efficacy of methadone that is still the most frequent drug utilized for the treatment of opioid withdrawal. One possible reason for the lack of evidence could be the difficulty in conducting trials with young people for to practical and ethical reasons. DETOXIFICATION TREATMENTS FOR OPIATE DEPENDENT ADOLESCENTS: Substance abuse among adolescents (13 to 18 years old) is a serious and growing problem. It is important to identify effective treatments for those who are opioid dependent. For adults, pharmacotherapy is a necessary and acceptable part of effective treatment. Detoxification agents are used to reduce withdrawal symptoms during managed withdrawal but the rate of completion of detoxification tends to be low, and rates of relapse are high. Withdrawal symptoms, particularly drug craving, may continue for weeks and even months after detoxification. The period of recovery from dependence is typically influenced by a range of psychological, social and treatment related factors. Detoxification treatments include methadone, buprenorphine, and alpha2-adrenergic agonists. Medications have been used less frequently in treating substance

abuse disorders among adolescents. The review authors searched the literature for controlled clinical trials investigating pharmacological interventions with or without psychosocial intervention aimed at detoxification in adolescents. They found only one US trial that compared 28-day treatment with buprenorphine, using tablets placed under the tongue, to wearing a clonidine patch in 36 opiate dependent adolescents who were treated as outpatients. The trial reported a trend in favour of buprenorphine in reducing the dropout rate but no difference between treatments in the duration and severity of withdrawal symptoms. More participants in the buprenorphine group went on to long-term naltrexone treatment. Side effects were not reported. Methadone is the most frequently used drug for the treatment of opioid withdrawal yet the review authors did not find any controlled trial using methadone. Conducting trials with young people may be difficult for both practical and ethical reasons

35. Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. Cochrane Database of Systematic Reviews 2009;(2):CD007210.
    Ref ID: 769
    Abstract: BACKGROUND: The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless no studies have been published which systematically assess the effectiveness of the pharmacological maintenance treatment among adolescent. OBJECTIVES: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on retaining adolescents in treatment, reducing the use of substances and reducing health and social status SEARCH STRATEGY: We searched the Cochrane Drugs and Alcohol Group's trials register (august 2008), MEDLINE (January 1966 to august 2008), EMBASE (January 1980 to august 2008), CINHAL (January 1982 to august 2008) and reference lists of articles SELECTION CRITERIA: Randomised and controlled clinical trials comparing any maintenance pharmacological interventions alone or associated with psychosocial intervention with no intervention, placebo, other pharmacological intervention included pharmacological detoxification or psychosocial intervention in adolescent (13-18 years) DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed trial quality and extracted data MAIN RESULTS: Two trials involving 187participants were included. One study compared methadone with LAAM for maintenance treatment lasting16 weeks after which patients were detoxified, the other compared maintenance treatment with buprenorphine - naloxone with detoxification with buprenorphine. No meta-analysis has been performed because the two studies assessed different comparisons. Maintenance treatment seems more efficacious in retaining patients in treatment but not in reducing patients with positive urine at the end of the study. Self reported opioid use at 1 year follow up was significantly lower in the maintenance group even if both group reported high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment at 12 month follow up. AUTHORS' CONCLUSIONS: It is difficult to draft conclusions on the basis of only two trials. One of the possible reason for the lack of evidence could be the difficulty to con-

duct trial with young people due to practical and ethic reasons. MAINTENANCE TREATMENTS FOR OPIATE DEPENDENT ADOLESCENTS: It is difficult to draw conclusions about the use of maintenance pharmacological interventions from only two trials. Substance abuse among adolescents (13 to 18 years old) is a serious and growing problem. The most common drugs used by young people worldwide are cannabis and inhalants. Psychostimulants (ecstasy and amphetamines), cocaine, LSD, heroin and other opioids are also used. Many adolescents who use heroin start by snorting it but some progress to injection. Heroin is used sporadically by the majority who use it, but it can become an addictive disorder. In adults, pharmacotherapy is a necessary and acceptable part of effective treatment for opioid dependence. Among adolescents, medications have been used infrequently and a choice has to be made between detoxification and maintenance treatment. The review authors searched the literature and identified two controlled trials from the USA that involved 187 heroin addicts, aged 14 to 21 years; the participants were treated as outpatients. One study of 37 participants compared methadone with LAAM for maintenance treatment. After 16 weeks of maintenance treatment the adolescents were detoxified. The two maintenance treatments gave similar improvements in social functioning. No side effects were reported. The second trial of 150 adolescents compared buprenorphine and naloxone as maintenance treatment with buprenorphine detoxification over 14 days. The maintenance treatment for nine weeks followed by tapered doses up to 12 weeks seemed to be more effective in retaining patients in treatment but not in reducing the use of drugs of abuse. At one-year follow up, self-reported opioid use was clearly less in the maintenance group and more adolescents were enrolled in other addiction programs. The most common side effect in both groups was headache. No participants left the study because of side effects. Conducting trials with young people may be difficult for both practical and ethical reasons

36. Moner SE. Acupuncture and addiction treatment. J Addict Dis 1996;15(3):79-100.
Ref ID: 1051
Abstract: RECORD STATUS: This record is a structured abstract written by CRD reviewers. The original has met a set of quality criteria. Since September 1996 abstracts have been sent to authors for comment. Additional factual information is incorporated into the record. Noted as [A:....]
AUTHOR'S OBJECTIVES: To review the evidence on how acupuncture works and to review the use of acupuncture for treatment of different drug dependencies
STUDY SELECTION - SPECIFIC INTERVENTIONS: The following types of acupuncture were studied: electro acupuncture, stud acupuncture, sutured bead, nonstimulated and laser. Control therapies included the following: methadone, counselling, sham acupuncture and sham electro acupuncture, ankle placebo, relaxation acupuncture, group therapy, laser probe placed near skin, placebo pill and no treatment
STUDY SELECTION - PARTICIPANTS: The participants studied were receiving treatment for opiate, alcohol, cocaine or tobacco dependency
STUDY SELECTION - OUTCOMES: The following outcomes were assessed: urine drug screen, Profile of Mood State, withdrawal symptoms, craving scale, self report on addictive behaviour, attendance for treatment, relapse rate, detoxification admission rate,

drinking episodes, cigarette smoking and abstinence
STUDY SELECTION - STUDY DESIGNS: Controlled trials of acupuncture were included
SEARCHING: Searches for published articles in the English language were made of MEDLINE, from 1976 to 1995 and of PsycLIT from 1990 to 1995, using the following search terms: 'alternative medicine' (exploded), 'acupuncture' (exploded), 'acupuncture therapy', 'acupuncture points', 'substance withdrawal syndrome', 'substance use disorders', 'addictive behaviour', 'substance abuse treatment centres' and 'substance dependence'. Bibliographies of published reviews on drug treatment and acupuncture were also searched
VALIDITY ASSESSMENT: The author does not state that they assessed validity
STUDY SELECTION - HOW WERE DECISIONS ON THE RELEVANCE OF PRIMARY STUDIES MADE?: The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection
DATA EXTRACTION: The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction
METHODS OF SYNTHESIS - HOW WERE THE STUDIES COMBINED?: The studies were combined in a narrative review
METHODS OF SYNTHESIS - HOW WERE DIFFERENCES BETWEEN STUDIES INVESTIGATED?: The author does not state how differences between the studies were investigated
RESULTS OF THE REVIEW: Three studies including one randomised controlled trial (RCT) were used to assess the effectiveness of acupuncture for opiate treatment (595 patients). Two studies including one RCT were used to assess the effectiveness of acupuncture for alcohol treatment (136 patients). Eight studies including 6 RCTs were used to assess the effectiveness of acupuncture for nicotine treatment (1,263 patients). One RCT was used to assess the effectiveness of acupuncture for cocaine treatment (108 patients). Opiate treatment: all of the trials had unacceptably high drop-out rates (ranging from 69 to 91%). The trials had variable lengths of follow-up and few defined what stage of treatment the study was to address. Alcohol treatment: the results were variable. The drop-out rates ranged from 47 to 100%. Nicotine treatment: none of the studies presented clear and consistent proof of the efficacy of acupuncture in smoking cessation. No study used biochemical markers to verify self-report of smoking abstinence. Cocaine treatment: the single study reported no significant difference between intervention groups. The drop-out rates were 80% at two weeks
AUTHOR'S CONCLUSION: The evidence for efficacy of acupuncture in drug treatment is very encouraging. Since acupuncture is quick, inexpensive and relatively safe, acupuncture treatment may establish itself as an important addition to addiction services in the future
CRD COMMENTARY: The discussion includes mention of some problems with the primary studies including: lack of assessment of outcomes such as withdrawal symptoms, relaxation or improvement in dysphoria; lack of comparison with conventional treatment; problems with the use of sham acupuncture as a control; and the use of variable doses and types of acupuncture. Some relevant details of the included studies are clearly pre-

sented in tabular format. By limiting the literature search to English language studies in two databases some relevant studies may have been omitted. No details are given of the methods used to select primary studies or to extract data. The inclusion criteria do not include a definition of the 'drug dependent' patient. It is not clear what criteria were used to select studies on nicotine treatment. The high drop-out rates reported are only mentioned relating to studies on opiate treatment and it is not clear if the data were analysed on an intention-to-treat basis. Given the lack of assessment of validity, the lack of clarity in the methods used to select primary studies and the high drop-out rates, the author's conclusions cannot be considered supported by the evidence given in this review

37. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA 1998;279(3):229-34.
Ref ID: 660
Abstract: OBJECTIVE: To review the scientific literature on the effectiveness of rapid opioid detoxification (RD) (opioid withdrawal precipitated by naloxone hydrochloride or naltrexone) and ultrarapid opioid detoxification (URD) (opioid withdrawal precipitated by naloxone or naltrexone under anesthesia or heavy sedation) techniques. DATA SOURCES: The MEDLINE database was searched from 1966 through 1997 using the indexing terms naloxone, naltrexone, substance dependence, and substance withdrawal syndrome. Additional data sources included bibliographies of papers identified on MEDLINE and bibliographies in textbooks on substance abuse. STUDY SELECTION: Inclusion criteria were studies of RD or URD, pharmacologic protocols specified, and clinical outcomes specified and reported. Exclusion criteria were unpublished data, data not in peer-reviewed journals, abstract-only publications, and review articles. DATA EXTRACTION: The methodologic characteristics of studies were extracted by the authors and summarized according to key components of research design concerning subject characteristics, therapy allocation, and outcomes assessed. DATA SYNTHESIS: A qualitative analysis was performed on the 12 studies of RD and the 9 studies of URD identified in our search. The RD studies enrolled 641 subjects (range for individual studies, 1-162): 7 were inpatient studies, and the protocols varied considerably, as did the outcomes assessed. Three RD studies included a control group, 2 used a randomized design, and 3 reported outcomes beyond 12 days. The URD studies enrolled 424 subjects (range for individual studies, 6-300): all were inpatient studies, the detoxification and anesthesia protocols varied, 3 included a control group, 2 used a randomized design, and 2 reported outcomes for URD beyond 7 days. CONCLUSIONS: The existing literature on RD and URD is limited in terms of the number of subjects evaluated, the variation in protocols studied, lack of randomized design and use of control groups, and the short-term nature of the outcomes reported. Further research is needed using more rigorous research methods, longer-term outcomes, and comparisons with other methods of treatment for opioid dependence. [References: 49]

38. O'Shea J, Law F, Melichar J. Opioid dependence. Clinical Evidence 2007;2007, 2007.
Ref ID: 278
Abstract: INTRODUCTION: Dependence on opioids is a multifactorial condition involving

genetic and psychosocial factors. There are three approaches to treating opioid dependence. Stabilisation is usually by opioid substitution treatments, and aims to ensure that the drug use becomes independent of mental state, such as craving and mood, and independent of circumstances, such as finance, and physical location. The next stage is to withdraw (detox) from opioids. The final aim is relapse prevention. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for stabilisation (maintenance) in people with opioid dependence? What are the effects of drug treatments for withdrawal in people with opioid dependence? What are the effects of drug treatments for relapse prevention in people with opioid dependence? We searched: Medline, Embase, The Cochrane Library and other important databases up to June 2006 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 21 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: buprenorphine, clonidine, lofexidine, methadone, naltrexone, and ultra-rapid withdrawal

39. Raisch DW, Fye CL, Boardman KD, Sather MR. Opioid dependence treatment, including buprenorphine/naloxone. Ann Pharmacother 2002;36(2):312-21.
Ref ID: 581
Abstract: OBJECTIVE: To review opioid dependence (OD) and its treatment. Pharmacologic treatments, including the use of buprenorphine/naloxone, are presented. Pharmaceutical care functions for outpatient OD treatment are discussed. DATA SOURCES: Primary and review articles were identified by MEDLINE and HEALTHSTAR searches (from 1966 to November 2000) and through secondary sources. Tertiary sources were also reviewed regarding general concepts of OD and its treatment. STUDY SELECTION/DATA EXTRACTION: Relevant articles were reviewed after identification from published abstracts. Articles were selected based on the objectives for this article. Studies of the treatment of OD with buprenorphine were selected based on the topic (pharmacology, pharmacokinetics, adverse reactions) and study design (randomized, controlled clinical trials in patients with OD with active/placebo comparisons and/or comparisons of active OD treatments). Articles regarding pharmacists' activities in the treatment and prevention of OD were reviewed for the pharmaceutical care section. DATA SYNTHESIS: OD is considered a medical disorder with costly adverse health outcomes. Although methadone maintenance treatment (MMT) is cost-effective for OD, only about 12% of individuals with OD receive this treatment. Psychological and pharmacologic modalities are used to treat OD, but patients often relapse. Drug therapy includes alpha 2-agonists for withdrawal symptoms, detoxification regimens with or without opioids, opioid antagonists, and opioid replacement including methadone, levomethadyl acetate, and buprenorphine. The Drug Addiction Treatment Act of 1999 allows for office-based opioid replacement therapies. Sublingual buprenorphine with naloxone can be used in

this milieu. Buprenorphine with naloxone is currently under new drug application review with the Food and Drug Administration. Clinical research shows buprenorphine to be equal in effectiveness to methadone, but safer in overdose due to its ceiling effect on respiratory depression. It has lower abuse potential and fewer withdrawal symptoms when discontinued. Naloxone is included to decrease diversion and injection of the tablets. Pharmacists in outpatient settings who are familiar with OD have opportunities to provide pharmaceutical care to patients receiving this treatment. Pharmaceutical care functions for OD include ensuring appropriate drug administration, monitoring adverse effects, alleviating withdrawal symptoms, treating intercurrent illnesses, minimizing diversion, and preventing relapse. CONCLUSIONS: OD is a critical unmet health problem in the US. Buprenorphine combined with naloxone represents an innovative treatment for OD in outpatient settings. This new treatment has advantages over MMT. [References: 83]

40. Roozen HG, Boulogne JJ, van Tulder MW, Van den Brink W, de Jong CAJ, Kerkhof AJFM. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. Drug Alcohol Depend 2004;74(1):1-13.
Ref ID: 512
Abstract: The community reinforcement approach (CRA) has been applied in the treatment of disorders resulting from alcohol, cocaine and opioid use. The objectives were to review the effectiveness of (1) CRA compared with usual care, and (2) CRA versus CRA plus contingency management. Studies were selected through a literature search of RCTs focusing on substance abuse. The search yielded 11 studies of mainly high methodological quality. The results of CRA, when compared to usual care: there is strong evidence that CRA is more effective with regard to number of drinking days, and conflicting evidence with regard to continuous abstinence in the alcohol treatment. There is moderate evidence that CRA with disulfiram is more effective in terms of number of drinking days, and limited evidence that there is no difference in effect in terms of continuous abstinence. Furthermore, there is strong evidence that CRA with "incentives" is more effective with regard to cocaine abstinence. There is limited evidence that CRA with "incentives" is more effective in an opioid detoxification program. There is limited evidence that CRA is more effective in a methadone maintenance program. Finally, there is strong evidence that CRA with abstinence-contingent "incentives" is more effective than CRA (non-contingent incentives) treatment aimed at cocaine abstinence. [References: 70]

41. Stanton MD, Shadish WR. Outcome, attrition, and family-couples treatment for drug abuse: a meta-analysis and review of the controlled, comparative studies. Psychol Bull 1997;122(2):170-91.
Ref ID: 665
Abstract: This review synthesizes drug abuse outcome studies that included a family-couples therapy treatment condition. The meta-analytic evidence, across 1,571 cases involving an estimated 3,500 patients and family members, favors family therapy over (a) individual counseling or therapy, (b) peer group therapy, and (c) family psychoeducation. Family therapy is as effective for adults as for adolescents and appears to be a cost-

effective adjunct to methadone maintenance. Because family therapy frequently had higher treatment retention rates than did nonfamily therapy modalities, it was modestly penalized in studies that excluded treatment dropouts from their analyses, as family therapy apparently had retained a higher proportion of poorer prognosis cases. Re-analysis, with dropouts regarded as failures, generally offset this artifact. Two statistical effect size measures to contend with attrition (dropout d and total attrition d) are offered for future researchers and policy makers

42. Tang YL, Zhao D, Zhao C, Cubells JF. Opiate addiction in China: current situation and treatments. Addiction 2006;101(5):657-65.
Ref ID: 410
Abstract: BACKGROUND: Historically, China has had extraordinarily high rates of opiate dependence. These rates declined drastically following the 1949 revolution; however, opiate abuse has re-emerged in the late 1980's and has spread quickly since then. AIMS: To describe the current situation of opiate addiction and treatments in China and make some suggestions. DESIGN: A descriptive study based on literature searched from Medline and the China National Knowledge Infrastructure database (1996 to 2004) and hand-picked references. FINDINGS: The number of registered addicts in 2004 was 1.14 million (more than 75% of them heroin addicts), but the actual number is probably far higher. Opiate abuse contributes substantially to the spread of HIV/AIDS in China, with intravenous drug use the most prevalent route of transmission (51.2%). Currently, the main treatments for opiate dependence in China include short-term detoxification with opiate agonists or non-opiate agents, such as clonidine or lofexidine; Chinese herbal medicine and traditional non-medication treatments are also used. Methadone maintenance treatment (MMT) has not been officially approved by the Chinese government for widespread implementation, but some pilot studies are currently underway. CONCLUSION: China faces substantial drug abuse problems that appear to be worsening with time. Opiate dependence is a major threat to the public health and social security of China because of its devastating medical effects, its impact on risk for HIV/AIDS and criminal behaviors, low rates of recovery and high rates of relapse. There is an urgent need to implement MMT and other modern treatments for opiate dependence more widely in China. [References: 80]

43. Torrens M, Fonseca F, Mateu G, Farre M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. Drug Alcohol Depend 2005;78(1):1-22.
Ref ID: 463
Abstract: Antidepressants are commonly used in substance abusers due to the potential effect on some underlying mechanisms involved in drug use disorders and to treat comorbid depression. A systematic review of the literature of the efficacy of antidepressant drugs in subjects with drug abuse disorders, including alcohol, cocaine, nicotine and opioid, with and without comorbid depression was performed. Only randomised, double-blind, controlled trials have been evaluated. A meta-analysis was done with the included studies that used common evaluation procedures in alcohol, cocaine and opioid dependence. Based on the present review some recommendations may be proposed. The prescription of antidepressants for drug abuse seems only clear for nicotine dependence

with or without previous comorbid depression (bupropion and nortryptiline). In alcohol dependence without comorbid depression, the use of any antidepressant seems not justified, while in cocaine dependence has to be clarified. The use of antidepressants in alcohol, cocaine or opioid dependence with comorbid depression needs more studies in well-defined samples, adequate doses and duration of treatment to be really conclusive. Interestingly, SSRIs do not seem to offer significant advantages compared with tricyclic drugs in substance abuse disorders. Differences both related to individual characteristics and specific antidepressant drugs need to be clarified in future studies. [References: 140]

44. Van den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2006;51(10):635-46. Ref ID: 394
    Abstract: OBJECTIVE: To provide an overview of treatment options for opioid-dependent patients. METHOD: We screened all published studies on the treatment of opioid dependence, with a special focus on systematic literature reviews, formal metaanalyses, and recent trials. RESULTS: Both clinical experience and neurobiological evidence indicate that opioid dependence is a chronic relapsing disorder. Treatment objectives depend on the pursued goals: crisis intervention, abstinence-oriented treatment (detoxification and relapse prevention), or agonist maintenance treatment. The high quality of solid evidence in the literature demonstrates that there are numerous effective interventions available for the treatment of opioid dependence. Crisis intervention, frequently necessary owing to the high overdose rate, can be effectively handled with naloxone. Abstinence-oriented interventions are effective for only a few motivated patients with stable living conditions and adequate social support. Agonist maintenance treatment is considered the first line of treatment for opioid dependence. Numerous studies have shown efficacy for methadone and buprenorphine treatment, while maintenance with other agonists is also becoming available to a greater extent. Maintenance treatment with diamorphine should be made available for the small group of treatment-resistant, severely dependent addicts. Other harm-reduction measures can serve to engage individuals with opioid addiction who are not in treatment. CONCLUSION: Opioid dependence is a chronic relapsing disease that is difficult to cure, but effective treatments are available to stabilize patients and reduce harm, thereby increasing life expectancy and quality of life. [References: 149]

PUBLIKASJONER FRA HÅNDSØK

Vi fant tre mulig relevante publikasjoner på nettsiden til national institute for health and clinical excellence (NICE).

Publikasjon 1 og 2

NICE has produced two guidelines on drug misuse – 'Drug misuse: psychosocial interventions' (NICE clinical guideline 51) and 'Drug misuse: opioid detoxification'

(NICE clinical guideline 52). They cover: the support and treatment people can expect to be offered if they have a problem with or are dependent on opioids, stimulants or cannabis how families and carers may be able to support a person with a drug problem and get help for themselves.
NICE clinical guideline 52 makes recommendations for the treatment of people who are undergoing detoxification for opioid dependence arising from the misuse of illicit drugs.

http://www.nice.org.uk/nicemedia/pdf/DrugMisuseOpioidDetoxFullGuidelinePublishedVersion.pdf

http://www.nice.org.uk/nicemedia/pdf/CG051NICEguideline2.pdf

Publikasjon 3 - Drug misuse - methadone and buprenorphine
Methadone and buprenorphine (given as a tablet or a liquid) are recommended as treatment options for people who are opioid dependent.

A decision about which is the better treatment should be made on an individual basis, in consultation with the person, taking into account the possible benefits and risks of each treatment for that particular person. If both drugs are likely to have the same benefits and risks, methadone should be given as the first choice.

Different people will need different doses of methadone or buprenorphine. People should take methadone or buprenorphine daily in the presence of their doctor, nurse or community pharmacist for at least the first 3 months of treatment and until they are able to continue their treatment correctly without supervision.

Treatment with methadone or buprenorphine should be given as part of a support programme to help the person manage their opioid dependence.

http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf